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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

LUNG CANCER — PART V
NON-SMALL-CELL LUNG CANCER-CURRENT MANAGEMENT STRATEGIES

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Non-small-cell lung cancer (nsclc) is a deadly disease with an overall 5-year survival of <17% in the USA, despite aggressive treatment programs. Initial treatment is dictated by disease stage at diagnosis. The most prevalent treatment for nsclc is surgery, if the cancer is operable. However, surgical resection is feasible in only 20% of patients with lung cancer because of disease stage and/or medical conditions that make resection unfeasible. The two other treatment modalities used routinely in the treatment of nsclc are radiation therapy (RT) and chemotherapy, administered alone, or in combination. There is increasing evidence that combined modality approaches, incorporating chemotherapy, RT and/or surgery, result in modest improvements in survival in locally advanced disease. Meta-analyses, and randomized studies have also shown that, in metastatic nsclc, chemotherapy results in improvements in both duration and quality of life (Clarke SJ and Boyer MJ, Respirology, Sep 1998;3(3):175-82).

Numerous clinical trials are ongoing to evaluate various combinations of these modalities, and novel therapies in all stages of nsclc. However, <1% of lung cancer patients are currently being treated in a clinical trial in the USA (Krasna MJ, etal, Ann Thorac Surg, Jul 1999;68(1):201-7).

Outcome of patients with nsclc is dismal with the majority ending up needing palliative care. One common and severe complication of lung cancer is airway obstruction, being represented by endoluminal or extraluminal stenosis, or a combination of both. These stenoses may be sometimes managed by external-beam RT but, more often, a minimally invasive procedure is used such as brachytherapy, laser therapy, electrocautery, cryotherapy, placement of airway stents, and balloon dilatation using bronchoscopic techniques.

EPIDEMIOLOGY BY AGE AND STAGE IN THE USA

Estimates of incidence at first diagnosis by age and stage are presented for the USA. Extrapolating these statistics to other areas, even in Europe, is impossible because they vary dramatically between world regions, and from country to country (see FO, p 1131).

Incidence of NSCLC by Gender and Age

As indicated in Exhibit 1, nsclc is most prevalent in males >65 years-of-age. In 2000, it is estimated that this population group accounts for 40% of all new cases in the USA. Overall, the incidence of nsclc in those over >65 years-of-age is 249/100,000 compared to 50/100,000 for those between the ages of 50 and 54, 91.5/100,000 in those between the ages of 55 and 59, and 148.5/100,000 in those between the ages of 60 and 64. Although those with good performance status (PS) have similar outcomes as younger patients, standard chemotherapy results in a higher morbidity in the elderly, prompting the evaluations of less toxic regimens. Therefore, this segment on nsclc patients represents a distinct target population for different treatment approaches.

Incidence of NSCLC by Stage

Staging of nsclc has been refined in recent years (see FO, p 1134), and treatment is becoming more relevant to disease status and prognosis. Incidence of nsclc by stage is estimated in Exhibit 2. These estimates reflect staging after surgical intervention that changes the initial staging by lowering Stage I populations, and increasing Stage II populations.

First-year and Five-year Survival by Stage

Exhibit 1 also estimates 1- and 5-year survival of nsclc patients in the USA by stage. As expected, patients with surgically verified Stage I disease have the best survival outlook, with 1-year mortality mostly attributed to operative and postoperative deaths, estimated at 1% and 4%, respectively. However, 5-year survival rates even for Stage I patients barely exceed 50%, while those of Stage IV patients are negligible.

Treatment Approaches by Stage

Traditionally, nsclc patients were either delegated to curative resection, or were treated primarily with palliative RT, with only 25% treated with chemotherapy. Currently, chemotherapy is being used increasingly in the treatment of locally advanced, or metastatic disease, and is being evaluated in a variety of settings as an adjuvant to surgery and/or RT in resectable disease, as a neoadjuvant approach to improve curative resection, and as a prevention of recurrence of early nsclc. Chemotherapy is also being increasingly employed in recurrent disease. Exhibit 3 estimates current USA nsclc populations by treatment modality by stage, and Exhibit 4 describes the various treatments in clinical use, and in development, for the various stages of nsclc.

SURGERY

Surgery is the standard curative intervention in early-stage nsclc, but surgical resection is feasible in only 20% of patients with lung cancer. Although in the USA, approximately 45% of all lung carcinomas are localized to the chest, surgery is only possible in less than half of these cases because of medical contraindications.

The two most effective surgical approaches are pneumonectomy involving the removal of all pulmonary lobes of one lung, or lobectomy. Although advances in perioperative management have improved outcome following pneumonectomy, the procedure carries a relatively high-risk. A 30-day mortality rate of 5% to 10% is reported in most modern series. A higher rate is expected for complex procedures. Pneumonectomy is also associated with a higher complication rate (predominantly cardiopulmonary in nature) than lesser resections (Klemperer J and Ginsberg RJ, Chest Surg Clin N Am, Aug 1999;9(3):515-25, vii).

Curative Surgery

Resection involving the affected lobe (lobectomy) is the gold standard in early stage nsclc. Limited surgical procedures, such as segmentectomy or wedge resection, are also being used but their effectiveness has been questioned. Sleeve resection may be used in Stage I disease where it results in a comparable survival to that of standard resection (Icard P, etal, Eur J Cardiothorac Surg, Apr 1999;15(4):426-32). However, limited surgery may adversely affect survival of patients with N+ disease. Therefore, pneumonectomy or lobectomy, are recommended when possible. Video-assisted thoracic surgery (VATS) is only used in the treatment of peripheral Stage Ia (T1N0) SCC <2 cm, but resections more limited than lobectomy are oncologically not adequate.

Although surgery is predominantly used in early disease, it may be useful in selected patients in more advanced disease. Also, various neoadjuvant regimens may make resection possible in patients originally presenting with inoperable nsclc.

Among 1,079 consecutive patients (males=877 and females=202) who underwent surgery for primary lung cancer at the Hopitaux Universitaires de Geneve in Switzerland, between January 1, 1977 and December 31, 1996, lobectomy was performed in 51.7% (n=558), while 29.6% (n = 319) of patients were treated with pneumonectomy, 6.8% with exploratory thoracotomy (n = 73), 6.3%

Exhibit I
Estimated Incidence of NSCLC by Gender and Age

Age Group	Male (#)	Female (#)	Total (#)	Male Rate*	Female Rate*	Total Rate*	Male (%)	Female (%)	Total (%)
≥39	695	552	1,253	.88	.71	.80	.880	1.050	.954
40-44	1,174	815	2,002	10.47	7.15	8.85	1.491	1.552	1.525
45-49	2,424	2,022	4,471	24.79	19.97	22.46	3.077	3.851	3.405
50-54	4,958	3,629	8,651	59.05	40.93	50.11	6.295	6.911	6.590
55-59	7,185	4,930	12,195	112.31	71.18	91.53	9.121	9.389	9.289
60-64	9,640	6,132	15,854	191.04	108.90	148.48	12.238	11.678	12.076
65-69	12,890	7,967	20,882	297.41	156.16	221.31	16.364	15.172	15.907
70-74	14,371	9,047	23,420	370.78	185.50	267.57	18.245	17.228	17.840
75-79	13,026	8,418	21,384	419.77	194.87	288.11	16.537	16.028	16.289
80-84	7,835	5,324	13,023	419.86	174.74	265.06	9.946	10.139	9.920
85+	4,570	3,676	8,145	353.27	121.81	188.90	5.804	7.001	6.205
Total	78,768	52,512	131,280	58.54	37.31	47.68	99.989	99.999	100.000
>65	52,692	34,432	86,854	364.08	169.09	249.33	66.896	65.568	66.160

** per 100,000*

with segmentectomy (n = 68) and 5.6% with bilobectomy (n = 61). In terms of histology, 57% of tumors (n=613) were SCC, and 30.3% were adenocarcinoma (n=327), while small-cell lung cancer (sclc) was diagnosed in 3% of patients (n=33). Overall operative mortality rate was 6.6%. The survival rate at 5 years was as follows, Stage Ia=61%, Stage Ib=43%, Stage IIa=37%, Stage IIb=19%, Stage IIIa=14%, Stage IIIb=0%, and Stage IV=4% (de Perrot M, etal, Schweiz Med Wochenschr, 17 Apr 1999;129(15):585-9).

A review of the charts of these 1,079 patients, divided into 5 equal 4-year periods (1977-1980, 1981-1984, 1985-1988, 1989-1992, 1993-1996), according to the year of surgery, revealed that the operative mortality significantly declined within the overall period from 9% to 4%, and the 5-year survival improved from 25% up to 40%. In the last two decades, a shift in histologic distribution was observed as well as an increasing proportion of patients with Stage I disease, a lower operative mortality, and a better 5-year survival. Between 1977-1980 and 1993-1996, the incidence of SCC declined significantly, whereas the incidence of adenocarcinoma and bronchioloalveolar carcinoma increased. The increasing number of Stage I disease at presentation, led to a higher proportion of lobectomies, and less extended lung resection (de Perrot M, Eur J Cardiothorac Surg, Apr 1999;15(4):433-7).

Between 1980 and 1994, 110 patients underwent bronchial sleeve lobectomy for bronchogenic cancer at Marie Lannelongue Hospital (Le Plessis Robinson, France). In 45 patients, preoperative investigations contraindicated pneumonectomy, whereas in 65 others, sleeve resection was the chosen alternative. The most common procedures were sleeve lobectomy of the right upper lobe (64%), and of the left upper lobe (21%); 16 patients (15%) underwent additional arterial vascular resection. In 6/7 patients with microscopic invasion of the bronchial margin further resection was not possible because of limited respiratory function. There were 32 Stage Ib (T2N0), 57 Stage IIb (T2N1), 17 Stage IIIa (8=T3N1 and 9=T2N2), and 4 *in situ* (Stage 0) cases. Operative mortality was 2.75%. The 5- and 10-year actuarial survival rates for the entire group were 39% and 22%, respectively. The 5-year actuarial survival rates were 60% in Stage Ib, 30% in Stage IIb, and 27% in Stage IIIa. The four factors that significantly influenced survival were nodal stage, arterial resection, invasion of the bronchial stump, and poor functional respiratory status contraindicating pneumonectomy (Icard P, etal, *ibid*).

Among 141 lung cancer patients surgically treated at Tampere University Hospital, in Finland, the perioperative mortality was 5.0 %; it was 2.4% among 84 patients operated with lobectomy, 5.6 % among 32 patients operated with pneumonectomy, and 0% in 25 patients operated with explorative thoracotomy. The 5-year survival of all patients, including perioperative mortality, was 33%. Survival was significantly better for 83 patients with Stage I disease (49%), than for 17 with Stage II (6%), 24 with Stage IIIa (20.8 %), and 17 with Stage IIIb/IV disease (0%). Survival was significantly better after lobectomy (44.1%), than after pneumonectomy (25.0%), or explorative thoracotomy (8.0%). Tumor histology did not affect survival. This study confirms the usefulness of surgery in Stage IIIa nsclc (Ikonen JT, etal, Ann Chir Gynaecol 1999;88(1):22-8).

Minimally invasive surgery is also being attempted in the treatment of lung cancer to minimize patient trauma associated with standard procedures. A technique, intrathoracic light-assisted anterior limited thoracotomy

(ILAALT), developed at Saiseikai Central Hospital (Tokyo, Japan), was shown to reduce duration of postoperative pain. The procedure involves an incision, 12 cm in length, below the breast. Subsequently, the pectoral major muscle is divided, and the fourth intercostal space is opened with a disconnection of the anterior cartilagenous portion. The posterior skin, including the serratus anterior muscle, is drawn posteriorly using a retractor. To illuminate the posterior and apex portions of the thoracic cavity, a flexible fiber light is introduced into the thoracic cavity through the eighth intercostal space at the posterior axillary line. In 28 lung resections with a mediastinal nodal dissection for lung cancer (24 lobectomies, 2 bilobectomies, and 2 pneumonectomies) that were performed without difficulty, the mean intrasurgical blood loss was 217 ml, the operative time 262 min, and chest tube drainage duration 2.3 days. Only one patient required a blood transfusion. All patients underwent continuous epidural anesthesia for 8 days postoperatively, and no analgesia was required after 14 days postoperatively (Nomori H, etal, Surg Today 1999;29(7):606-9).

Video-assisted thoracic surgery (VATS) is performed using 3 small incisions on the side of the chest through which the entire anatomic pulmonary lobe, as well as all peribronchial lymph nodes, and anterior hilar lymph nodes may be removed. VATS is presently not advocated for definitive treatment of lung cancer; rather, it is mostly used in staging and diagnosis of disease. Although cervical mediastinoscopy remains the gold standard for precise mediastinal lymph-node staging, VATS may replace anterior mediastinoscopy, is useful in taking biopsies of lymph nodes not accessible by cervical mediastinoscopy, and may be a means of judging the resectability of the primary tumor. Also, precise diagnosis of solitary pulmonary nodules is possible by VATS, but protective measures must be taken to prevent spillage of tumor cells (Van Schil P, Acta Chir Belg, May-Jun 1999;99(3):103-8).

In an ongoing phase II clinical trial (protocol ID: CLB-39802), sponsored by the NCI and being conducted by the Cancer and Leukemia Group B (Scott J Swanson, Chair), a total of 135 patients with solitary, small (<3.0 cm), peripheral nsclc (no metastasis or positive lymph nodes at mediastinoscopy), accrued over 3 years, are being treated with VATS lobectomy. If it is not possible to remove the lobe using VATS then one of the incisions is converted to a standard thoracotomy. Patients are followed every 4 months for the first 2 years, and then every 6 months for the next 3 years. The objectives of the trial are to:

- determine the feasibility of performing VATS lobectomy, without significant morbidity or perioperative mortality
- determine the rate at which a thoracotomy must be carried out to complete a VATS lobectomy
- describe the complications associated with this procedure
- describe the length of the operative procedure, duration of chest tube stay, and length of hospitalization
- assess overall and failure-free survival of VATS-operated patients over a 5-year period

In a prospective trial, conducted in Japan, to compare the long-term prognosis of VATS lobectomy with conventional lobectomy in Stage Ia (T1N0M0) nsclc, 100 consecutive patients underwent either conventional lobectomy through open thoracotomy (n=52), or VATS lobectomy (n=48) between January 1993 and June 1994. Lymph-node dissections were performed in a similar manner in both groups. Pathologic N1 and N2 disease was found in 3 and 1 patients, respectively, in the thoracotomy group, and in 2 and 1 patients, respectively, in the VATS group. During follow-up, distant metastases and local/regional recurrences developed in 7 and 3 of the thoracotomy group, respectively, and in 2 and 3 in the VATS group, respectively. Also, 2 patients in the thoracotomy and 1 in the VATS group developed second primary cancers. The overall 5-year survival rate after surgery was 85% in the thoracotomy group, and 90% in the VATS group. Therefore VATS lobectomy with lymph node dissection achieved an excellent 5-year survival, similar to that achieved by the conventional approach (Sugi K, etal, World J Surg, Jan 2000;24(1):27-30; discussion 30-1).

Surgery in Lung Metastases

Lung metastasectomy seems to be a safe and effective treatment option even for patients who show further metastases. Among 93 patients with lung metastases operated on from 1983 to 1997, surgical complications occurred in eight (9%); seven (8%) were operated on again because of further lung cancer, and two (3%) died in the hospital. Overall, average survival after metastasectomy was 40 months (median=22 months). Actuarial survival was 44% at 3 years and 35% at 5 years. Overall survival with metastasectomy, after treatment of the primary tumor, was 87 months (median=58 months) while actuarial survival was 58% at 5 years and 38% at 10 years. The average time between treatment of primary tumor and disease-free interval (DFI) before metastasectomy was 4 years (median=41 months). Patients with a DFI >2 years lived longer. There were 23 patients with nonepithelial and 70 patients with epithelial tumors who experienced similar DFIs (mean=47, median=34 months for non-epithelial, and mean=51, median=29 months for epithelial tumors). Among those with nonepithelial tumors, 38% survived for 5 years. Results of metastasectomy did not differ considerably by primary tumor site with 5-year survival rates of 20% for kidney tumors, 28% for colorectal cancer, 30% for soft-tissue sarcoma, 28% for skin melanoma, and 18% for breast cancer. According to this study it seems that, except for breast carcinoma (which has a slightly worse prognosis), the results of surgical resection are not dependent on either the location, or the histologic pattern of the primary tumor (Koodziejski L, etal, Eur J Surg Oncol, Aug 1999;25(4):410-7).

Exhibit 2
Estimated Stage Distribution at Diagnosis and 1-year and 5-year Survival of NSCLC Patients by Stage in the USA in 2000

	Incidence (#)	Total (%)	Total by Stage (%)	1-year Survivors (#)	1-year Survival Rate (%)	5-year Survivors (#)	5-year Survival Rate (%)
Stage I	13,128	10.0	100.0	12,472	95.0	6,877	52.4
Stage Ia	4,411	3.4	33.6	4,190	95.0	2,867	65.0
Stage Ib	8,717	6.6	66.4	8,281	95.0	4,010	46.0
Stage II	26,255	20.0	100.0	24,942	95.0	9,233	35.2
Stage IIa	2,993	2.3	11.4			1,556	52.0
Stage IIb	23,262	17.7	88.6			7,676	33.0
Stage III	39,383	30.0	100.0	21,660	55.0	4,726	12.0
Stage IIIa	19,691	15.0	50.0	12,799	65.0	3,741	19.0
Stage IIIb	19,691	15.0	50.0	8,861	45.0	985	5.0
Stage IV	52,510	40.0	100.0	18,379	35.0	1,050	2.0
Total	131,275	100.0		77,452	59.0	21,886	16.7

** These estimates are based on a variety of sources including SEER data and reflect staging at first diagnosis and after surgical staging.*

RADIOTHERAPY (RT)

Radiotherapy (RT) is a common treatment approach in nsclc (Exhibit 3), used in a variety of settings (Exhibit 4). Over 50% of nsclc patients are treated with first-line RT alone, or in combination with surgery and/or chemotherapy (chemoradiotherapy). RT is particularly helpful in early inoperable disease, and is also used for palliation in late-stage disease. One of the theories behind the use of RT in locally advanced nsclc is that improved local tumor control reduces/delays incidence of distant metastasis. Various approaches of RT delivery are being used such as external beam RT, intensity modulated RT (IMRT); and brachytherapy, among others.

However, use of postoperative RT to prevent recurrence in completely resected nsclc may do more harm than good. In a randomized multinational clinical trial of postoperative RT, involving 728 patients who underwent complete resection for Stage I/II/III nsclc, the 5-year survival rate was only 30% in the RT group, compared with 43% among controls managed only by observation. RT increased the rate of noncancer deaths in a dose-dependent manner, and did not significantly prevent either recurrence or metastasis (Dautzenberg Bertrand, etal, Cancer 1999;86:195-196,265-273). Although this trial's investigators discourage use of postoperative RT in this setting, and recommend reserving optimized RT only to those at a high risk of local recurrence because of incomplete resection, others believe that this study's unfavorable results may have been influenced by several inherent limitations.

External Beam Radiotherapy

Standard external beam RT involves delivery of 30 fractions of 2 Gy for a total dose of 60 Gy in 6 weeks. Other external beam RT approaches include 3-dimensional conformal RT, accelerated RT, fractionated RT, hypofractionated RT, hyperfractionated RT, hypofractionated accelerated RT (HART), continuous hyperfractionated accelerated RT (CHART), etc. One of the challenges of external beam RT is delivery of a therapeutic dose of radiation to the tumor and, at the same time, sparing healthy tissue. Currently, dosing is based on radiobiology and empirical data derived from clinical trials. Because delivery of higher radiation doses has been shown to increase local control in lung cancer, various approaches are used to maximize such delivery to the tumor. One of the dose-limiting factor in RT of lung cancer is lung parenchyma. Investigators from Universita degli Studi (Milano, Italy) have used single photon emission computed tomography (SPECT) for lung perfusion studies to map functioning lung parenchyma with higher sensitivity than CT in order to design radiation beams that minimize irradiation of functioning lung. With this approach, optimal design of irradiation field geometry decreased the area of functional parenchyma exposed to high doses; sparing was greater with smaller irradiation volumes. Functional data provided by SPECT lung perfusion was integrated into a commercial irradiation planning system that spares larger areas of functional lung parenchyma (Cattaneo GM, etal, Radiol Med (Torino), Apr 1999;97(4):272-8).

Between January 1980 and December 1995, 156 chemonaive patients with Stage I inoperable nsclc were irradiated at Duke University Medical Center and the Veterans Affairs Hospital (Durham, NC). Median dose of RT was 64 Gy (50 Gy to 80 Gy) administered in 1.2 Gy *bid* to 3 Gy *qid* fractionation. Among 141 evaluable patients (T1N0=54%, T2N0=46%; SCC=52%, adenocarcinoma 18%, large cell carcinoma=19%, other=11%), 108 died (35% of cancer). At last follow-up, 33 patients were alive (MST=24

Exhibit 3
First-line Treatment of NSCLC by Stage in 2000

Stage	Chemotherapy (#)	Chemotherapy (%)	Radiation (#)	Radiation (%)	Surgery (#)	Surgery (%)
Stage I	788	6.0	3,019	23.0		
Stage II	3,938	15.0	13,128	50.0		
Stage III	14,611	37.1	26,583	67.5		
Stage IV	18,904	36.0	32,556	62.0		
Total*	38,240	26.3	75,286	51.8	26,255	20.00

* *Reflects multimodality therapies*

months, range=7-132 months) with cause-specific MST of 30 months and a 2-year survival of 60%, and a 5-year survival of 32%. The 2- and 5-year overall survival was 39% and 13%, respectively. On multivariate analysis, significant factors influencing overall and/or cause-specific survival were age, SCC histology, incidental diagnosis, and pack-years of smoking. There was a nonsignificant trend towards improved cause-specific survival with higher RT doses, and larger treatment volumes. Uncontrolled lung cancer was the primary cause of death, and local failure alone represented the most common mode of failure (42%). Patients who were locally controlled had a significantly improved cause-specific survival over those who failed locally. Regarding patterns of failure, 42% of failures were local only, and 38% were distant only. Regional-only failure occurred in 4 patients (7%), 3 of whom failed solely in an unirradiated nodal site. Significant factors associated with a lower local failure at 2 years included incidental diagnosis, and absence of cough with a strong trend toward significance for higher RT dose and larger treatment volume. Patients who were locally controlled had an improved cause-specific survival at 5 years (46%) over those who were not controlled (12%). Grade 3/4 complications occurred in 2 (1.5%) patients (Sibley GS, etal, Int J Radiat Oncol Biol Phys, 1 Jan 1998;40(1):149-54).

In node-positive (N+M0), accelerated RT alone (45 Gy at 3 Gy per fraction) produced similar results as standard RT (60-66 Gy at 2 Gy per fraction) in regard to response rates, locoregional control, and overall survival. Given the fact that accelerated treatment schedules decrease treatment time and cost less, it may be more cost-effective to treat patients with locally advanced nsclc, and borderline poor prognostic factors, with this approach (Nguyen LN, etal, Int J Radiat Oncol Biol Phys, 15 Jul 1999;44(5):1053-6).

Hyperfractionated RT when used in Stage II nsclc patients who are not suitable for or refuse surgery, results in better outcomes than those experienced with standard RT. According to a retrospective analysis of the records of 67 chemotherapy- or immunotherapy-naive patients with operable nsclc (43 had medical contraindications, and 24 refused surgery), treated between 1988 and 1993 with hyperfractionated radiotherapy with 1.2 Gy twice daily to a total dose of 69.6 Gy, after a median follow-up period of 61 months, MST was 27 months, and the 5-year survival rate was 25%; the 5-year local control rate was 44%. There were 2 bronchopulmonary and 2 esophageal acute Grade 3 toxicities, and 1 bronchopulmonary and 2 esophageal late Grade 3 toxicities; there was no Grade 4/5 toxicity (Jeremic B, etal, Radiother Oncol, May 1999;51(2):141-5).

CHART, which uses 36 fractions of 1.5 Gy, 3 times per day, to administer 54 Gy in 12 consecutive days was found to be superior to conventional RT in achieving local tumor control, and improving survival in locally advanced nsclc. In a 563-patient, multicenter, randomized, controlled trial that compared CHART with conventional RT in patients with nsclc, conducted in the UK between April 1990 and April 1995, CHART was found to be superior to conventional RT in terms of survival with a hazard ratio=0.78. This translates to 22% reduction in the relative risk (RR) of death, which is equivalent to an absolute improvement of 9%, from 20 to 29% in the 2-year survival rate, and a 21% reduction in the RR for local progression. Among patients with SCC (81% of cases), there was a 30% reduction in RR of death, which is equivalent to an absolute improvement of 13% in the in 2-year survival rate, from 20% to 33%, and a 27% reduction in RR of local progression. Furthermore, in SCC, there was a 25% reduction in RR of local and/or distant progression and a 24% reduction in RR of metastasis. This demonstrates the importance of cellular repopulation as a cause of failure in the radiotherapy of nsclc (Saunders M, Radiother Oncol, Aug 1999;52(2):137-48).

Hypofractionated RT achieved symptom control in the majority of patients with inoperable advanced nsclc. A hypofractionated RT schedule using 20 Gy in 5 fractions was used to treat 52 inoperable patients with Stage IIIb/IV nsclc. Approximately one month after RT, those (n=19) who achieved a >50% reduction in tumor load and respiratory symptoms, all Stage IIIb, were treated with a similar second course of 20 Gy for a total dose of 40 Gy. Overall, 2-year survival rates were 10% for Stage IIIb and 0% for Stage IV patients. Survival rates at 1 and 2 years were 33% and 0%, respectively, in the group of patients treated with 20 Gy, and 52% and 21%, respectively, in those treated with 40 Gy. Among the patients that were irradiated with a dose

of 20 Gy, a subjective reduction of dyspnea and cough, and remission of hemoptysis were observed in 97%, 82% and 80% cases, respectively. Complete remission of dyspnea and coughing was observed in 17 (89%) and 14 (74%) patients treated with two irradiation courses, respectively. Treatment-related toxicity was mild. Early evaluation after 20 Gy allowed selection of responsive patients that could benefit from more prolonged treatment (Donato V, etal, Tumori, May-Jun 1999;85(3):174-6).

A clinical trial comparing external beam RT with other endobronchial approaches in palliation of endobronchial obstruction failed to produce results when it became impossible to recruit the 400 patients necessary to obtain statistically significant results. In this trial, patients with predominantly intraluminal obstruction of the trachea, a main bronchus, or a lobar bronchus by unresectable nsclc, were being randomized to external beam RT or the clinician's choice of endobronchial treatment with brachytherapy, laser resection or cryotherapy, according to local availability and practice. However, only 75 patients were randomized from 7 centers over 3.5 years, and enrollment was abandoned in November 1996 (Moghissi K, etal, Clin Oncol (R Coll Radiol) 1999;11(3):179-83).

Intensity Modulated Radiation Therapy (IMRT)

Intensity modulated radiation therapy (IMRT) can treat difficult to reach tumors such as lung malignancies with an increased level of accuracy. Radiation doses up to 40% higher than those possible with traditional methods can be delivered without any negative impact in 70% or more of the surrounding healthy tissue. IMRT may also be used to treat patients with locally recurring tumors after exposure to conventional RT. Although for some patients, IMRT replaces external beam procedures, in most cases, IMRT is used in conjunction with or after another primary treatment. The two ways IMRT differs from conventional radiation are:

- IMRT uses a powerful, advanced computer program to plan a precise 3-dimensional radiation dose, based on individual tumor size, shape and location
- IMRT directs radiation at the tumor and modulates the intensity of pencil-thin beams of radiation with laser accuracy

Brachytherapy

Brachytherapy (also see FO, pp 792-4, 703-4, 295) that involves a brief introduction of a source of radiation in the bronchi, may be effective both in the treatment of tracheal bronchial malignancy, including primary and recurrent bronchogenic carcinoma, and metastatic carcinoma, and also in cases where there is compression caused by a tumor outside the bronchi. Intraluminal brachytherapy is effective in palliating complications caused by malignant endobronchial tumors such as dyspnea, hemoptysis, intractable cough, atelectasis, and postobstructive pneumonia. Brachytherapy may be used repeatedly, and also in patients undergoing external beam RT.

Intraluminal brachytherapy involving the introduction of a radioactive source into a polyethylene afterloading catheter using fiberoptic bronchoscopy has replaced interstitial implantation of radioactive sources directly to the tumor using rigid bronchoscopy. Although brachytherapy has been shown to be an effective and safe palliative treatment for endobronchial malignancies, further investigation is necessary to determine optimal treatment strategy in terms of dose delivered to the tumor and in determining what other modalities such as external beam RT, surgery, chemotherapy, or other endobronchial procedures such as Nd:YAG laser therapy, or cryotherapy may be combined with this twechnique.

Endobronchial brachytherapy may be indicated in patients with endobronchial mural disease, or tumors that extend beyond the bronchial wall. Although there is a risk of severe complications with brachytherapy, it is more a function of the location of the tumor being treated rather than the treatment itself. When the tumor involves the mainstem bronchi and upper lobes, it may be necessary, before attempting brachytherapy, to use CT scanning to exclude tumor invasion of the pulmonary arteries, or considerable destruction of the bronchial wall and mediastinal invasion of the tumor (Sheski FD and Mathur PN, Clin Chest Med, Mar 1999;20(1):123-38).

Endobronchial high-dose-rate (HDR) brachytherapy using iridium-192 (^{192}Ir) seeds, is an established technique in the treatment of advanced malignant airway obstruction when used in conjunction with endobronchial laser resection, and may also be effective when all other options are exhausted. HDR endobronchial brachytherapy is effective both for preventing and relieving malignant endobronchial obstruction, and can affect a cure in carefully selected patients (Escobar Sacristan, etal, Arch Bronconeumol, Jun 1997;33(6):278-83). Although there were few acute complications, there was an incidence of 21% of fatal hemorrhages, probably the result of patient selection rather than a treatment-related complication (Macha HN, etal, Lung 1995;173(5):271-80).

Among 346 patients (SCC=65%) with obstructing endobronchial malignancies treated at Lungenklinik (Hemer, Germany) by endobronchial HDR ^{192}Ir afterloading between 1983 and 1993, a palliative effect was achieved in about 66% of patients, even after all types of conventional interventions such as external beam RT, had been exhausted. The protocol involved endobronchial HDR brachytherapy, performed on an outpatient basis, at a dose of 5 Gy at 10 mm from the source axis administered on 3 occasions in 365 patients with the objective of palliation, and on 4 occasions in 19 patients to affect a cure, at intervals of 14 days. MST was 9 months for limited disease and 5 months for extensive disease.

Intraoperative brachytherapy may also be effective in early-stage high-risk nsclc medically ineligible for resection. From January 8, 1997 to March 16, 1998, 23 patients with Stage I nsclc at high risk for conventional surgery

because of cardiopulmonary compromise underwent combined VATS and intraoperative placement of ^{125}I seeds embedded in vicryl mesh at Allegheny General Hospital (Pittsburgh, PA).

Seeds embedded in vicryl suture were attached with surgical clips to a sheet of vicryl mesh, and thoracoscopically inserted over the target area with nonabsorbable suture or surgical clips. A total dose of 100-120 Gy prescribed to the periphery of the target area was delivered. Mean target area covered was 48 cm^2, mean total activity was 22 mCi and median length of postoperative stay was 7 days.

After a median follow-up of 11 months, there was no dislodgment of the seeds verified by postoperative CT and no local recurrence in any patient. However, 3 patients developed distant metastasis and 1 developed an ipsilateral recurrence in the right lower lobe after undergoing a right upper lobe resection. There were 3 postoperative deaths attributable to medical comorbid conditions, or surgical complications. Pulmonary function testing performed 3 months after implantation revealed no significant difference between preoperative and postoperative values (Chen A, etal, Int J Radiat Oncol Biol Phys, 15 Jul 1999;44(5):1057-63).

Proton-beam Radiotherapy

Proton-beam RT appears safe in early-stage nsclc with good DFS and local control that compare favorably with published reports using conventional RT. This approach is particularly appropriate in patients with compromised cardiopulmonary function because proton beams can be targeted more accurately than x-rays and, therefore, the dose administered can be significantly reduced to help prevent pulmonary damage.

In a prospective study undertaken at Loma Linda University Medical Center (Loma Linda, CA), between July 1994 and March 1998, 37 nsclc patients (Stage I=27, Stage II=2 patients and Stage IIIa=8 patients) who were not candidates for surgical resection for medical reasons or because they refused treatment, were treated either with 45 Gy to the mediastinum and gross tumor volume with photons, and a concurrent proton boost to the gross tumor volume of an additional 28.8 cobalt gray equivalents (CGE), for total tumor dose of 73.8 CGE over 5 weeks if they had adequate cardiopulmonary function (n=18), or with proton-beam RT to the gross tumor volume only, with 51 CGE administered in 10 fractions over a 2-week period if they had poor cardiopulmonary function (n=19).

No significant toxicities were encountered except 2 patients in the proton and photon arm developed pneumonitis that resolved with oral steroids. Follow-up of evaluable patients ranged from 3 to 45 months, with a median of 14 months. Actuarial DFS at 2 years for the entire group was 63%; for Stage I patients, DFS at 2 years was 86%. Local disease control was 87% (Bush DA, etal, Chest, Nov 1999;116(5):1313-9).

CHEMOTHERAPY

In the past, it was believed that chemotherapy would not play a role in nsclc, largely because alkylating agent-based therapies produced severe side effects, actually shortening survival. However, in the 1980s, randomized clinical trials showed that platinum-based chemotherapy improved patient survival, and quality of life (QoL), by relieving symptoms in the majority of patients. Cisplatin-based chemotherapy was the first therapy to show that survival could be improved by such an approach. For instance, before cisplatin chemotherapy became available, MST of patients with Stage IV disease was extremely poor, ranging between 16 to 17 weeks, with only 10% to 15% of these patients alive at 1 year. Randomized trials that compared best supportive care, including palliative RT, with cisplatin-based combination therapy, showed a modest improvement in the survival of these patients with MST rising by 10 weeks, from 16 to 26 weeks, and the 1-year survival rate by 10%, from 15% to 25%. Cisplatin-based therapies also relieved symptoms and improved QoL at an acceptable cost, which was sometimes lower than the cost associated with best supportive care (Bunn PA Jr, etal, Semin Oncol, Aug 1998;25(4 Suppl 9):2-10).

Since then, treatment with 4 new agents, paclitaxel, docetaxel, gemcitabine, and navelbine, approved in the 1990s for the treatment of nsclc (Exhibit 5), when compared to platinum monotherapy in phase II trials, resulted in higher response rates, and longer survival. In randomized trials, combinations of cisplatin and paclitaxel, or gemcitabine, or vinorelbine, improved survival in advanced disease when compared to cisplatin alone, or cisplatin in combination with etoposide. The toxicity profile of the new agents is also favorable compared to cisplatin-based therapy. Preliminary results of chemotherapy in earlier stages of nsclc are also encouraging. Thus, currently available chemotherapy regimens, administered to nsclc patients with good performance status (PS), can improve survival to a similar extent as in other solid tumors (Bunn PA Jr and Kelly K, Clin Cancer Res, May 1998;4(5):1087-100).

When cytotoxic chemotherapy was evaluated in terms of survival in a meta-analysis using updated data on 9,387 (7,151 deaths) patients with early, locally advanced, and advanced nsclc, enrolled in 52 randomized trials (both published and unpublished) conducted in the UK, France and Italy, results from modern regimens containing cisplatin favored chemotherapy in all comparisons, and reached conventional levels of significance when combined with radical RT, and with supportive care. Drug regimens used in the trials varied considerably, with overlap of drugs across regimens. In advanced disease, chemotherapy tripled the l-year survival rate to 15% compared with 5% for standard supportive care, and increased MST from 1 month to 2.5 months. Trials comparing supportive care with supportive care plus chemotherapy produced a hazard ratio of 0.73, representing a 27% reduction in the risk of death, and a 10% improvement in the 1-

Exhibit 4
Treatment Options and Prognosis by Stage

Stage 0 (carcinoma *in situ*)
It is recommended that resection is performed using the least extensive technique possible (segmentectomy or wedge resection) to preserve maximum normal pulmonary tissue because patients are at high risk for second lung cancers; endoscopic photodynamic therapy (PDT) may be used for very early central tumors that extend <1 centimeter within the bronchus (Furuse K, etal, J Clin Oncol 1993, 11(10):1852-57; Edell ES and Cortese DA, Chest 1992, 102(5):1319-1322; Patelli M, etal, Monaldi Arch Chest Dis, Aug 1999;54(4):315-8)
Stage I
Lobectomy, or segmental, wedge, or sleeve resection, or VATS, are used as appropriate; patients with smaller tumors fare better with surgery; visceral pleural invasion does not seem to influence survival. Histologic type is also a significant prognostic variable, with SCC having a better prognosis than non-SCC tumors. Other prognostic factors that influence survival are age and gender, and completeness of resection. For operable patients, prognosis is adversely influenced by presence of pulmonary symptoms, tumor size >3 cm, erbB-2 oncoprotein, K-ras gene mutations, vascular invasion, and increased numbers of blood vessels in the tumor specimen (Harpole DH, etal, Cancer Research 1995, 55(1):51-56, Slebos RJ, etal, NEJM 1990, 323(9):561-565, and Fontanini G, etal, J Pathology 1995, 177:57-63). Among 365 patients with clinical Stage I disease who underwent resection at National Cancer Center Hospital East (Chiba, Japan), between January 1987 and December 1994, the overall 3-year and 5-year survival rates were 78.1% and 66.5%, respectively (Suzuki K, etal, Ann Thorac Surg, Apr 1999;67(4):927-32)
RT with curative intent is used for potentially resectable disease with medical contraindications to surgery. For inoperable patients treated with RT, cause-specific 3- and 5-year survival was 60%, and 32% (median=30 months), respectively; recurrence rate is 28% to 45%. Higher doses of RT appear to provide improved local control
Adjuvant chemotherapy following resection for chemoprevention, and endoscopic PDT (under clinical evaluation in highly selected T1N0M0 patients) are being evaluated in clinical trials (Furuse K, etal, *ibid*)
Stage Ia (T1N0M0)
Surgery with lobectomy, pneumonectomy, or segmental, wedge, or sleeve resection, or VATS is used as appropriate. Prognosis is excellent with surgery alone, with 5-year survival rates as high as 70%, but patients are at high-risk of developing second primary lung cancer, and distant metastases
Stage Ib (T2N0M0)
Surgery (as above) is used in appropriate candidates. Prognosis is good with a 5-year survival rate of about 60%; distant metastases represent about 65% of all causes of relapse; however, according to a multivariate analysis, T2 status and high preoperative serum carcinoembryonic antigen (CEA) levels were independent significant factors indicative of a poor prognosis with a hazard ratio of 2.20 and 1.88, respectively; patients with both of these factors experienced a 3-year and 5-year survival rates of 65% and 38%, respectively, and risk of death for this subgroup was 4.14-fold than that of the overall clinical Stage I population; for a subgroup with high preoperative serum CEA levels, a complete preoperative staging workup, and multimodal therapy, especially induction chemotherapy, instead of surgical intervention alone, could be beneficial (Suzuki K, etal, *ibid*)
Stage II
Surgery (as in Stage Ib) or RT with curative intent (for potentially operable patients with medical contraindications to surgery) are standard treatment approaches. Clinical trials of adjuvant chemotherapy with or without other modalities following curative surgery are ongoing, but RT following curative surgery to control residual disease was not shown effective in clinical trials (Lung Cancer Study Group, J Clin Oncol, Jan 1988;6(1):9-17); 5-year survival rate is 30%-60% with distant metastases representing about 74% of all causes of relapse
Stage IIa (T1N1M0)
Surgery alone, or RT alone in inoperable N0 disease are standard interventions. According to a retrospective review of 92 evaluable patients who underwent complete resection for T3N0M0 disease, from 1979 to 1993, at Mayo Clinic (Rochester, MN), the actuarial 2- and 4-year overall survival rates for the entire cohort were 48% and 35%, respectively, and the actuarial local control at 4 years was 94%; local control and overall survival did not depend on primary tumor location, type of surgery performed, or use of adjuvant RT (Gould PM, etal, Int J Radiat Oncol Biol Phys, 1 Aug 1999;45(1):91-5)
Stage IIb (T2N1M0;T3N0M0)
Stage T2N1 nsclc that involves the nodes is best treated by complete resection with mediastinal lymphadenectomy; as in Stage I, tumor size and histology are significant prognostic variables; 5-year survival after complete resection ranges between 40% and 50%; postoperative RT may improve local control, while chemotherapy results in a slightly reduced risk of death (Deslauriers J and Gregoire J, Chest, Apr 2000;117(4 Suppl 1):104S-9S)
Stage III
Patients with poor prognostic factors are usually treated with RT alone. Standard treatment for unresectable or medically inoperable Stage III nsclc and good prognostic factors, is induction chemotherapy followed by definitive RT to the primary site at 1.8-2.0 Gy per fraction with a total dose of 60-63 Gy to the target volume. Recent clinical trials indicate that concurrent RT and MVP chemotherapy (see Exhibit 6) yields a significantly higher response rate, and result in a longer MST when compared with the sequential approach (Furuse K, etal, ASCO00, Abs. 1893), a fact also demonstrated in a retrospective analysis of nsclc patients treated at Hoag Cancer Center (Newport Beach, CA) during the 1990-1997 period (Dillman RO, ASCO00, Abs. 2079)

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Cisplatin-based induction chemotherapy before surgery, or RT, was shown to improve survival of patients with Stage III nsclc. In a small patient sample, paclitaxel was effective as a radiosensitizer when administered with RT after induction chemotherapy with cisplatin (Morales S, etal, ASCO00, Abs. 2154)

Proton-beam RT may be indicated in inoperable disease in patients with poor cardiopulmonary function

Stage IIIa (T1N2M0; T2N2M0; T3N1M0; T3N2M0)

Surgery alone is used in highly selected cases (in one prospective series survival in T3N2M0 disease was 7%); chemotherapy is combined with other modalities. Results with preoperative MVP [cisplatin (120 mg/m^2 or 25 mg/m^2/week), vinblastine, and mitomycin] for Stage IIIa patients with clinically apparent mediastinal (N2) disease have been encouraging. Other approaches used include surgery with postoperative RT or RT monotherapy.

Among 222 patients with N2 disease, multivariate analyses revealed 3 significant prognostic factors, incomplete resection, larger tumor size, and multiple diseased N2 nodes; while overall 5-year survival was 27%, the 5-year survival of 32 N2 patients with pathologic multiple N2 nodes was 5%, whereas it was 57% in 76 patients with neither N2 disease nor multiple N2 nodes (Suzuki K, etal, J Thorac Cardiovasc Surg, Jul 1999;118(1):145-53). In a retrospective analysis of 150 cases of bronchogenic Stage IIIa nsclc, treated with pneumonectomy (n=70), lobectomy (n=61), lobectomy with associated atypical resection (n=9), atypical resection (n=6), and bilobectomy (n=4), the 5-year survival rate was 16.9%; it was 29.7% for pneumonectomy and 26.8% for lobectomies associated with atypical resection (Briccoli A, etal, Minerva Chir, Apr 1999;54(4):219-23); overall 5-year survival is 15% to 29%

Superior sulcus tumor and other chest wall tumors (T3N0/N1M0)

Survival of patients with lung cancer invading the chest wall after resection with curative intent relies highly on the extent of nodal involvement, and the degree of completeness of resection, and to a much lesser extend on the depth of chest wall invasion (Downey RJ, etal, Ann Thorac Surg, Jul 1999;68(1):188-93). Local therapy may be curative, especially in T3N0 disease; treatment options include RT and surgery, RT alone, or surgery alone (selected cases), or chemotherapy combined with other modalities such as brachytherapy (Miller JI and Phillips TW, Annals of Thoracic Surgery 1990;50(2):190-196). Clinical trials of combined modality therapy, and neoadjuvant chemotherapy are ongoing

Stage IIIb (any T, N3M0; T4, any N, M0)

Treatment options include RT alone, chemoradiotherapy; neoadjuvant chemotherapy and concurrent RT followed by resection, or chemotherapy alone

Malignant pleural effusion (MPE)

Multimodality therapy, consisting of surgery and chemoradiotherapy, or PDT, are current options for the treatment of MPE; chemical pleurodesis, or sclerosis, involves instilling a sclerosing agent such as bleomycin, doxycycline, or talc into the pleural space after fluid drainage; Sclerosol that introduces sterile talc into the pleural space with an aerosolized application process, supplied by Bryan, was approved in January 1998 for the prevention of recurrence of malignant pleural effusions in symptomatic patients

Stage IV (any T, any N, M1)

External-beam RT is used primarily for palliative relief of local symptomatic tumor growth. Combination chemotherapy with cisplatin/vinorelbine, or cisplatin (or carboplatin)/paclitaxel, or cisplatin/gemcitabine, or triple-agent chemotherapy with cisplatin/vinblastine/mitomycin, are being evaluated in clinical trials as well as novel chemotherapy agents/regimens. Endobronchial laser therapy, or brachytherapy may be useful in managing obstructing lesions. Patients with good PS, women, and those with distant metastases confined to a single-site appear to live longer (Albain KS, etal, J Clin Oncol 1991, 9(9): 1618-26). In the case of brain metastases, that affect 1/3 of nsclc patients, standard treatment involves whole brain irradiation to palliate symptoms. However, more aggressive approaches such as surgical resection and stereotactic radiosurgery, have dramatically improved control of brain metastases and have resulted in a meaningful survival outcome for a subset of eligible patients; chemotherapy may also have a role in the treatment of brain metastases (Kelly K and Bunn PA Jr, Lung Cancer, May 1998;20(2):85-91)

Recurrent nsclc

RT, or chemotherapy alone (for chemonaive patients, regimens are as in Stage IV nsclc), are used for palliation/salvage. Interestingly, surgical resection of isolated cerebral metastasis, or stereotactic radiosurgery, are possible in highly selected patients. Laser therapy, or interstitial RT, may be used for management of endobronchial lesions. Various drugs, alone or in combinations and multimodality approaches, are in clinical trials (Exhibit 6), including docetaxel monotherapy, and a regimen of epirubicin and gemcitabine that may be a reasonable alternative as second-line chemotherapy following platinum failure (Van Putten JWG, etal, see Exhibit 6)

Lung Cancer Metastasized from Other Primary Sites

Lung metastasectomy is possible in selected patients. According to a retrospective analysis of the records of 4,572 patients accrued by the International Registry of Lung Metastases since 1991, who underwent complete surgical lung metastasectomy, after a mean follow up was 46 months, the disease-free interval was 0 to 11 months in 1,729 (33%) cases, 12 to 35 months in 1,857 (36%) and more than 36 months in 1,620 (31%). Actuarial survival after complete metastasectomy was 36% at 5 years, 26% at 10 years and 22% at 15 years (MST=35 months); the corresponding values for incomplete resection were 13% at 5 years and 7% at 10 years (MST=15 months). Among complete resections, the 5-year survival was 33% for patients with a disease free-interval of 0 to 11 months, and 45% for those with a disease-free interval of more than 36 months; 43% for single lesions and 27 for four or more lesions (Friedel G, etal, Zentralbl Chir 1999;124(2):96-103). Also, thoracic metastasectomy for germ cell tumors may achieve permanent cure of chemoresistant disease; according to a retrospective analysis of 141 consecutive patients who underwent resection of thoracic metastases at Royal Brompton Hospital (London, UK), the overall survival was 77% at 5 years, and 65% at 15 years (Cagini L, etal, Ann Oncol, Nov 1998;9(11):1185-91)

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Exhibit 5
Novel Chemotherapeutics Approved in the USA for the Treatment of NSCLC

Amifostine (Ethyol; MedImmune Oncology)
USA Approval
An sNDA was approved in March 1996 under FDA's accelerated approval program for reduction of cumulative renal toxicity associated with repeated administration of cisplatin in the treatment of nsclc. Ethyol was first approved in the USA in December 1995 for the same indication in advanced ovarian cancer
Clinical Trials and Results
In metastatic disease, results from a phase II trial of 25 patients with previously untreated metastatic nsclc indicated that amifostine (740 or 910 mg/m^2) potentiated the activity of cisplatin (120 mg/m^2) and vinblastine (5 mg/m^2), administered in weekly doses; 15 of 21 (71%) evaluable patients had an objective PR to the 3-drug combination. Survival at 6 and 12 months was 85% and 65%, respectively. Toxicities included Grade 3 renal dysfunction (14%) and Grade 3 (10%) and Grade 4 (90%) neutropenia (Schiller JH, etal, ASCO95, Abs.1084:356)
In a phase II trial, designed to assess the feasibility and toxicity of amifostine (740 mg/m^2), the drug was administered prior to paclitaxel (225 mg/m^2) infused over 3 hours and carboplatin (AUC=6) in the initial 15 patients; subsequently, the second amifostine infusion prior to carboplatin was deleted. A total of 57 cycles of chemotherapy, and 98 amifostine infusions were delivered to 21 patients. Grade 3/4 neutropenia occurred in 5%/5%, thrombocytopenia in 7%/2%, and anemia in 11%/0%, respectively; Grade 1/2/3/4 neuropathy occurred in 22%/9%/9%/-, myalgia/arthralgia in 7%/7%/5%/-, nausea/vomiting in 45%/11%/2%/; alopecia in 36%/40%/-/-, and malaise in 27%/13%/4%/- and 7/57 (12%) cycles were complicated by hospitalization (only 1 hospitalization was related to amifostine induced toxicity-hypotension). Of the 98 amifostine infusions, 6 were interrupted for hypotension, one for vomiting and 26% and 24% were complicated by acute nausea and vomiting, respectively. Among 19/21 evaluable patients CR rate was 5%, and PR rate was 36%, while disease stabilized in 16%, and progressed in 43%. MST was 4.6 months with a 1-year survival of 15%. Although amifostine was associated with acceptable toxicity, its effect on cumulative toxicity remains unclear (Socinski MA, etal, ASCO99, Abs. 2015). Results from other trials did not support a role for amifostine in platinum-based chemotherapy in nsclc. In a phase II clinical trial, amifostine (740 mg/m^2) administered IV over 15 minutes followed immediately by IV paclitaxel (200 mg/m^2) infused over 60 minutes, followed immediately by IV carboplatin (AUC=6), infused IV over 30 minutes did not have a major impact on the neurotoxicity of the carboplatin/paclitaxel regimen (Mitchell RB, etal, ASCO99, Abs. 2322:601a)
Among patients with a poor prognosis Stage IIIb/IV nsclc, treated with the mitomycin/ifosfamide/cisplatin (MIP) regimen, amifostine did not prevent acute or cumulative renal, neurological or hematological toxicities, possibly because of the low numbers of treatment cycles performed, the quite low toxicity of this regimen, and the short median patient survival times (Souquet PJ, ASCO99, Abs. 1882:488a). Similar results were reported with high-dose paclitaxel (Robinson J, ASCO99, Abs. 2337:605a). One study, however, reported favorable results by the addition of amifostine to a cisplatin plus vinorelbine regimen (Manzione L, etal, ASCO99, Abs. 1925:499a)
Amifostine appears to prevent significant esophagitis and pneumonitis associated with concurrent RT and a paclitaxel/carboplatin regimen in nsclc. In a phase II clinical trial, paclitaxel (170 mg/m^2), administered over 3 hours, and carboplatin (AUC=5), administered every 4 weeks for 3 cycles, were combined with conformal RT (6100 cGy) and amifostine, administered with chemotherapy at a dose of 740 mg/m^2, and at 200 mg/m^2, with RT, on days 4 and 5. Among 20 patients with histologically proven, unresectable nsclc (Stage II=1, Stage IIIa=7, Stage IIIb=12, and SCC=10, adenocarcinoma=7 and other types=3), entered in the trial between October 1996 and November 1998, at the University of Cincinnati (Cincinnati, OH), in 43 cycles of chemotherapy (35 with amifostine), Grade 3 toxicities were neutropenia (n=10), nausea/vomiting (n=3), thrombocytopenia (n=2), esophagitis (n=2), pneumonitis (n=1). Hypersensitivity reactions, attributed to amifostine, were seen in 9 patients, leading to discontinuation in 4. Among 15 patients evaluable for response, there were 3 (20%) CR and 10 <CR (disease progressed in the brain during therapy in 2 patients) and 10 patients died (one free of disease) with the longest survivor alive at 25 months. MST was 15 months. Amifostine allowed use of concurrent paclitaxel, carboplatin and RT by decreasing the incidence of esophagitis and pneumonitis. The combination was well tolerated and active in locally advanced, unresectable nsclc (Roychowdhury DF, etal, ASCO99, Abs. 2011:522a)
Between October 1997 and August 1999, 68 patients with previously untreated Stage IIIa/IIIb nsclc were randomized so that 36 were treated with paclitaxel (60 mg/m^2), and 35 with carboplatin (AUC=2), once weekly during a 5 to 6 weeks course of RT (2 Gy) delivered daily for 5 days per week, alone (n=32), or with amifostine (300 mg/m^2) administered before chemotherapy (n=36), and daily before RT. The study, conducted at Metaxas Cancer Hospital (Athens, Greece), was designed to evaluate the role of amifostine in the prevention of esophagitis, and lung and other toxicities arising from RT and cisplatin chemotherapy. Amifostine significantly reduced the incidence of Grade ≥3 acute esophagitis from 88% to 47%, and Grade ≥3 lung toxicity from 59% to 21% in the paclitaxel arm, and from 80% to 29% and 53% to 18%, respectively in the carboplatin arm. Incidence of Grade ≥3 pneumonitis at 3 months among 45 patients, was 7/23 in the amifostine arm compared to 14/22 in the control arm. ORR (CR+PR) was 32% with paclitaxel, and 36% with carboplatin in the amifostine arm, and 26% and 32%, respectively, in the control arm (Antonadou D, etal, ASCO00, Abs. 1960)
Market
USA sales in 1999 were $48.3 million and off-shore sales were $24.2 million, bringing total worldwide sales to $72.5 million. Ethyol is marketed in the USA by Alza (Palo Alto, CA) and co-promoted by MedImmune Oncology (West Conshohocken, PA), and is marketed in Europe by Schering-Plough, and in Canada by Eli Lilly

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Docetaxel (Taxotere; Aventis)
USA Approval
An sNDA for docetaxel for treatment of locally advanced or metastatic nsclc, resistant to platinum-based therapy, was filed in the USA in December 1998 and, in December 1999, the FDA expanded approval of Taxotere to include treatment of cisplatin-resistant nsclc; Taxotere was approved for this indication in the EU in January 2000 after it was recommended by the CPMP in October 1999; to date, Taxotere has been approved in 50 countries for this cancer indication
Clinical Trials and Results
Compilation of data from phase II trials of single-agent docetaxel therapy in advanced nsclc, yielded overall response rates of 26% and a 1-year survival rate of 52%. In a phase III clinical trial, patients with Stage IIIb/IV nsclc that progressed after previously administered platinum-based chemotherapy, were randomized to docetaxel (100 mg/m^2 or 75 mg/m^2), every 3 weeks, or vinorelbine (30 mg/m^2) weekly, or ifosfamide (2 gm/m^2) for 3 days, every 3 weeks. There was no limit to the number of prior chemotherapy cycles/regimens administered, and those previously treated with paclitaxel for brain metastases were also eligible. Among 373 patients enrolled at 23 sites, 350 were evaluable. Response rates were 12% and 8% for the 100 mg/m^2 and 75 mg/m^2 for docetaxel regimens, respectively and 1% for the vinorelbine or ifosfamide regimen, and response was unrelated to prior paclitaxel exposure. TTP favored the docetaxel regimens, and MST was 5.6 months in all 3 arms, but the 1-year survival was 32% with the docetaxel regimen compared to 10% with vinorelbine or ifosfamide. Incidence of Grade 4 neutropenia/infection were 77%/12% in the docetaxel 100 mg/m^2 group, 54%/7% in then 75 mg/m^2 and 30%/1% in the vinorelbine/ifosfamide group. There were no differences in other toxicities, or in toxicity-related deaths, or treatment discontinuation (Fossella FV, etal, ASCO99, Abs 1776:460a, and Anticancer Drugs, Nov 1999;10 Suppl 1:S25-8)
Although single-agent docetaxel is active as salvage therapy in pretreated relapsed advanced nsclc, toxicities are generally high, resulting in Grade 4 neutropenia in 80% of patients and febrile neutropenia requiring IV antibiotics and hospitalization in 15%. In a phase III clinical trial, conducted to assess the impact of single-agent docetaxel on response, survival, and QoL, in nsclc patients previously treated with platinum-based chemotherapy, 204 patients were randomized to Taxotere (49 patients at 100 mg/m^2 and 55 patients at 75 mg/m^2) or best supportive care (BSC; 100 patients). A planned interim analysis of the first 100 patients showed an ORR of 8.6% (median duration=24 weeks). MST was 5.9 months with Taxotere versus 4.9 months with BSC, and QoL assessments (pain and fatigue) were statistically significantly better compared to BSC. There were 3 deaths. Febrile neutropenia and neutropenic infections occurred in 20% and 24% of patients, in the 2 docetaxel arms but incidence of Grade 3/4 nonhematologic toxicity, or other severe adverse events, was comparable (Shepherd F, etal, ASCO99, Abs 1784:463a). According to final results, MST of patients treated with the 75 mg/m^2 dose was 9.0 months compared to 4.6 months for those on BSC, and MTP was 12.3 weeks versus 7 weeks. The 1-year survival rate was 40% at the 75 mg/m^2 dose level, compared to 16% in the BSC group. Patients treated with Taxotere used less RT and symptom-relieving medications, and experienced less weight loss, less pain and fatigue, and had more appetite
In order to reduce this high docetaxel toxicity, in a phase II clinical trial, IV docetaxel (100 mg/m^2) was administered on day 1, every 3 weeks, for a maximum of 6 cycles, in combination with primary prophylactic subcutaneous lenograstim (5 mg/kg), on days 4 to 10, 23 pretreated patients with Stage IIIb (n=3) and Stage IV (n=20) nsclc. Main toxicity was Grade 2/3 fatigue in 10/2 patients, Grade 4 cutaneous in 1 patient, Grade 3 neutropenia in 2 patients with no cases of Grade 4 neutropenia or febrile neutropenia. There were 5 (21.7%) PR. Median time to progression and MST were 3 and 5 months, respectively (Barletta E, etal, ASCO00, Abs. 2137)
Docetaxel has also been used in the neoadjuvant setting, and as a radiosensitizer, but its effect appears minimal. In a multinational phase III clinical trial, 258 patients with Stage IIIa/IIIb radically-untreatable nsclc, were randomized to arm A(n=127), treated with docetaxel (100 mg/m^2), administered by 1-hour infusion, every 3 weeks, for 3 consecutive cycles (total=347 cycles) followed with definitive local treatment (surgery=22 and RT=74), or to arm B (n=131), treated immediately by definitive local treatment (surgery=29 and RT=102). Major toxicity in arm A was Grade 4 neutropenia (34% of cycles); 3.9% of patients in arm A experienced febrile neutropenia (1.4% of cycles), and 3.2% Grade 3/4 infections with 2 deaths attributable to infection. The ORR was 31.5% in arm A, with 1-year survival rate of 60%, and an MST of 15.6 months, 17.8 months for patients with Stage IIIa N2, 17.4 months for patients with Stage IIIa T3, and 13.6 months for patients with Stage IIIb. In arm B, 1-year survival rate was 56%; MST was 13.7 months, 14.4 months for patients with Stage IIIa N2, 13.7 months for patients with Stage IIIa T3, and 12.5 months for patients with Stage IIIb (Mattson KV, etal, ASCO00, Abs. 1890)
Numerous combinations of docetaxel with other chemotherapeutics have been, or are being evaluated in phase II or phase III clinical trials (Exhibit 6) as first-line therapy for advanced nsclc. Results of studies using docetaxel plus irinotecan suggest that this is a promising combination. In a phase I study, conducted at the Mayo Clinic, 3/5 patients who were treated with irinotecan, followed by docetaxel, experienced a PR. In a phase I clinical trial, conducted at Yale Cancer Center (New Haven, CT), escalating doses of docetaxel (25 to 40 mg/m^2) were administered before irinotecan (50 mg/m^2) for 4 weeks, followed by a 2-week rest. There was one PR among 5 (1/4 chemonaive patients) evaluable patients
Market
Worldwide sales were $520 million in 1999, up 43.2% from 1998; worldwide sales were $124.1 million in 1Q00, up 57.8% from 1Q99, excluding currency effects (71% otherwise)

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Gemcitabine ❑ Gemzar (Eli Lilly)

USA Approval

Gemzar was approved in the USA, in September 1998, for treatment of locally advanced or metastatic nsclc, as monotherapy, or in combination with cisplatin

Clinical Trials and Results

Approval of gemcitabine in nsclc was based in a phase II clinical trial of 53 patients, concluded in 1997, that showed that the drug, administered in combination with cisplatin, resulted in a higher response rate and increased survival time when compared to standard combination therapies. Among 50 evaluable patients gemcitabine plus cisplatin resulted in an overall response rate of 52%, consisting of two CR (4%) and 24 PR (48%) and MST was 13-16 months compared to a response rate of 30%-40%, and an MST of 8 months for standard combination (Abratt RP, etal, J Clin Oncol, Feb 1997, 15(2):744-9)

An independent review of gemcitabine monotherapy trial results, showed that the drug is active against nsclc, a claim subsequent confirmed in larger-scale studies. Four pivotal, open-label phase II clinical trials of advanced nsclc, with response rate as the primary endpoint, were designed to provide accurate, consistent, reproducible response rates. Chemonaive patients with Stage III/IV nsclc were treated in 3 of these trials with gemcitabine (800 or 1250 mg/m^2), administered once-weekly, for 3 weeks, followed by a rest week, and in the fourth trial with gemcitabine (90 mg/m^2), administered twice-weekly, for 3 weeks, every 4 weeks. Independent review reduced responders from 114 (30%) of 374 evaluable patients to 79 (21%), with the response range reduced from 25%-35% to 20%-23% after validation (Gwyther SJ, etal, Anticancer Drugs, Sep 1999;10(8):693-8)

A phase II multicenter clinical trial of gemcitabine monotherapy was undertaken to assess its efficacy and toxicity of gemcitabine in 50 nsclc patients (platinum-sensitive=15, platinum-refractory=35) who progressed/relapsed after treatment with platinum (cisplatin or carboplatin)-containing regimens). Gemcitabine (1000 mg/m^2) was delivered on days 1 and 8 of a 21-day cycle with a median of 4 courses administered (range 2-8). Among 43 patients (platinum-sensitive=11, platinum-refractory=32), evaluable for response, and 50 for toxicity, there was 1/32 (3%) CR and 3/32 (9%) PR, with disease stabilizing in 10/32 (31%) and progressing in 18 (56%) in the platinum-refractory, and 1/11 (9%) PR, with disease stabilizing in 6/11 (54%), and progressing in 4 (36%) in the platinum-sensitive group; median progression-free survival was 3.1 months and 5.4 months and MST was 8.6 months and 13.1 months, respectively. Treatment was well tolerated with no treatment-related deaths. Toxicity was principally hematologic with Grade 3 neutropenia occurring in 23% of patients and Grade 4 thrombocytopenia in 12%. Encouraging survival and stable disease rates may reflect activity of gemcitabine not detected by measurable tumor response, or an indolent growth pattern in this patient cohort (Law L, etal, ASCO00, Abs. 2095)

Gemcitabine is being evaluated in numerous combination trials in nsclc (Exhibit 6). The combination of gemcitabine and platinum achieved response rates, and extended survival data, comparable to other two-drug combinations such as paclitaxel/carboplatin, cisplatin/vinorelbine, and cisplatin/tirapazamine. A clinical trial of a 3-drug regimen of gemcitabine, cisplatin and vinorelbine is on-going (FO, pp 1070-1). Other drugs used in combination with gemcitabine include docetaxel (FO, p 1066 and Rizvi NA, etal, Semin Oncol, Oct 1999;26(5 Suppl 16):27-31; discussion 41-2), vinorelbine, etoposide and paclitaxel, among others

Market

Worldwide sales of Gemzar were $456 million in 1999, up 49% from the comparable 1998 period. The drug has been approved in over 65 countries worldwides

Paclitaxel ❑ Taxol (Bristol-Myers Squibb)

USA Approval

Taxol has been approved as first-line therapy, in combination with cisplatin, for advanced nsclc that cannot be treated by surgery or RT. It was recommended for approval in the USA, in March 1998, and was approved in June 1998; it was also approved in Europe in October 1998, and in Japan in January 1999

Clinical Trials and Results

The paclitaxel and cisplatin or carboplatin combination regimen has evolved as the standard in advanced nsclc. In a 332-patient phase III EORTC trial in advanced nsclc, cisplatin (80 mg/m^2) on day 1 was administered either in combination with paclitaxel (175 mg/m^2), as 3-hour infusion on day 1 (Arm A), or teniposide (100 mg/m^2), on days 1, 3, and 5 (Arm B). Hematologic toxicity was more severe in arm B; Grade 3/4 leukopenia, neutropenia and thrombocytopenia were 19%/66%, 54%/83%, 2%/36%, in arms A and B, respectively, which led to more febrile neutropenia (3%/27% in arms A and B, respectively), dose reductions and treatment delays. Grade 2/3 myalgia was 17%/5%, but Grade 3/4 peripheral neurotoxicity was more frequent in arm A (14%/5% in arms A and B, respectively). Hypersensitivity reactions and cardiac toxicity were negligible in both arms, and other toxicities were comparable. There were 2 CR and 66 PR (44%) in arm A, and 1 CR and 46 PR (30%) in arm B. There were 11 early toxic deaths (3 and 8 on arms A and B, respectively) and 210 patients died post-treatment. MST in arms A and B were 9.4 months and 9.7 months, respectively. Arm A was superior to arm B in response rate, side effects and QoL. Although MST did not improve, arm A represented a better palliative treatment for advanced nsclc than arm B (Giaccone G, etal, ASCO77, Abs. 1653:429a)

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In the largest randomized phase III clinical trial (E1594) to date in advanced nsclc, conducted by the Eastern Cooperative Oncology Group (ECOG) under PI Joan Schiller, MD, of the University of Wisconsin Comprehensive Cancer Center (Madison, WI), between October 1996 and May 1999, that enrolled 1,207 patients with previously untreated Stage IIIb or Stage IV nsclc, the reference regimen of cisplatin (75 mg/m^2) on day 1 and paclitaxel (175/mg/m^2) over 24 hours, was compared to 3 platinum-based regimens consisting of gemcitabine (1000 mg/m^2), on days 1, 8, 15 plus cisplatin (100 mg/m^2) on day 1, or docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2), both on day 1, or paclitaxel (225 mg/m^2), over 3 hours plus carboplatin (AUC=6), both on day 1. At an interim analysis, the study was closed to PS 2 patients because of excessive toxicity on each of the 3 cisplatin arms. Because small variances in effectiveness and toxicity were expected between these previously evaluated regimens, a large number of patients, about 300 for each arm, needed to be enrolled. The study was designed to provide statistically significant comparisons of each of the 3 experimental arms to the standard arm of paclitaxel plus cisplatin, but not to compare the experimental arms to one another. There were no significant differences in the response rates between any of the 3 experimental regimens, and the control regimen. Among 1,146 (Stage IIIb=98 and Stage IV=968) evaluable patients, the ORR was 18.5% and overall time to progression was 3.6 months. There were no significant differences in the TTP, except for the gemcitabine plus cisplatin arm, which had a longer 1-month median TTP compared with the other arms (4.5% versus 3.3% to 3.6%). Overall survival was essentially identical in all 4 arms; overall median survival was 7.8 months, and overall 1-year survival rate was 33.5, and the 2-year survival rate was 12%. However, there were both statistically, and clinically relevant differences in toxicities associated with these 4 regimens. Overall, the paclitaxel plus carboplatin regimen was the least toxic, with Grade 4/5 toxicities ocurring in 57% of cases, compared to 66% to 70% in the other regimens. Grade 4/5 toxicities involving absolute neutrophil (white blood cell) count (ANC), vomiting, and neuropathy, were 68%/4% in the paclitaxel plus cisplatin regimen, 69%/4% in gemcitabine plus cisplatin, 61%/6% in docetaxel plus cisplatin, and 53%/3% in the paclitaxel plus carboplatin. As of November 1999, 743/1,070 (69.4%) enrolled patients had died. In addition to a lower toxicity rate, the paclitaxel plus carboplatin, and docetaxel plus cisplatin regimens were more convenient as both drugs in the combination were administered on day 1, every 3 weeks (Schiller JH, etal, ASCO00, Abs. 2)

The combination of paclitaxel and carboplatin was also effective in locally advanced disease. In a 38-patient clinical trial, conducted at the University of Pittsburgh Cancer Institute, patients with locally advanced nsclc were treated with weekly low-dose paclitaxel (45 mg/m^2), as a 3-hour infusion, combined with weekly carboplatin (100 mg/m^2) and simultaneous standard-dose thoracic radiotherapy. Overall, the regimen was well tolerated. The one-year actuarial survival rate of this group was 63%, with 2 and 3 year rates estimated at 54% (Belani CP, etal, ASCO97, Abs. 1608:448a)

Paclitaxel has also been investigated in 3- and 4-drug combination trials (Exhibit 6). A dose-intensive 4-drug combination regimen involving ifosfamide, carboplatin, etoposide, and paclitaxel (ICE-T), was evaluated in a phase II clinical trial (FO, p 1071)

Market

Worldwide sales were $1,481 million in 1999, up 23% from 1998. Worldwide sales in the 1Q00 were $385 million, up 17% from 1Q99

Porfimer sodium (Photofrin; Axcan)

USA Approval

Photofrin was approved in the USA in January 1998 for early-stage microinvasive endobronchial nsclc in patients who are not indicated for surgery and/or RT and, in December 1998, for palliation of obstructing endobronchial nsclc; in July 1997 QLT (Vancouver, Canada) filed a sNDA with the Canadian Health Protection Branch which was approved in July 1999. The submission was supported by data from clinical trials involving 650 patients in Canada, USA and Europe. Photofrin was approved for this indication in Japan in 1978

Clinical Trials and Results

Reports from clinical studies show that Photofrin provides long-term tumor responses in more than 50% of patients with early-stage superficial lung cancer. In clinical trials, approximately three quarters of patients experienced CR following treatment, with about half of them being cancer-free in long-term follow-up

Among 26 patients with inoperable nsclc (all were previously treated with external irradiation, Nd-YAG laser and/or brachytherapy) treated with IV Photofrin II (2 mg/kg), 10/11 Stage I patients achieved a CR, with the remaining 1 patient, and 11/15 Stage III patients achieving a PR; 4 patients, 2 of whom were exposed to inadequate illumination, did not respond. Thus, the objective response rate was 85% (22/26). Although lung function did not improve, dyspnea was ameliorated in 7 (58%) of those with a PR; disease progressed in 4 Stage III patients who died of pulmonary hemorrhage 1.5-6 months after PDT. Grade 1/2 skin photosensitivity was seen in 4 patients. Although of value in Stage I nsclc, the clinical benefit of PDT in Stage III disease appears small (Sutedja T, etal, Eur J Cancer 1992;28A(8-9):1370-3)

A total of 102 unresectable patients (prior resection=47%, poor pulmonary function=42%, multilobar tumors=20%), or tumors affecting the proximal airways=11%) with superficial lung cancer who were usually radiologically occult, were enrolled in 3 trials, conducted at British Columbia Cancer Agency (Vancouver, Canada), and at Free University Hospital (Amsterdam, The Netherlands), to study the efficacy and safety of PDT as a potentially curative treatment for patients. Photofrin (2 mg/kg) was administered IV followed 2 days later by illumination of the tumor area with red light of 200 J/cm of tumor length. Clean-up bronchoscopy was routinely performed 2 days after light application to remove necrotic tissue. Histologic CR was achieved in 79% of patients, and disease did not recur in more than half of them after follow-up of more than 2 years. MST was 3.5 years, and the disease-specific MST was 5.7 years. The most frequent adverse events were photosensitivity reactions (22%) which were usually like a mild to moderate sunburn. Other adverse events included mucous exudate (22%), local edema (18%), and dyspnea (7%). Most adverse events were mild to moderate and self-limiting (Lam S, etal, ASCO98, Abs. 1781:463a)

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Market
Worldwide sales were $10.9 million in 1999, an increase of 24% versus $8.8 million in 1998. In June 2000, QLT announced it sold worldwide rights of Photofrin to Axcan Pharma (Mont-Saint-Hilaire, Quebec, Canada) for an initial net cash payment of CAN$2.5 million, 1,283,333 common shares of Axcan and CAN$13.5 million in preferred shares of Axcan redeemable within 12 months in cash, or additional common shares. In addition, QLT is entitled to a deferred payment of CAN$4 million, and milestone payments based on future events of up to CAN$20 million, payable in cash or preferred shares. Concurrent with the completion of the sale, QLT paid approximately 45% of this consideration to Sanofi-Synthelabo in respect to the latters's marketing rights to Photofrin in the USA, in a similar combination of Axcan common shares, Axcan preferred shares, and cash
Vinorelbine tartrate (Navelbine; Glaxo SmithKline)
USA Approval
Vinorelbine was approved in the USA, in December 1994, as first-line monotherapy for advanced nsclc. The drug is available worldwide; it has been approved and launched for this indication in Europe in June 1998, in Japan in February 1999, and in Canada, and China, among other countries
Clinical Trials and Results
The usual initial dose of Navelbine monotherapy is 30 mg/m^2, administered weekly as an IV injection over 6 to 10 minutes. According to results from the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS), a phase III clinical trial that compared treatment with vinolebine and best supportive care with best supportive care alone, single-agent vinorelbine improved survival and possibly improved overall QoL of elderly patients (≥70 years-of-age) with advanced (Stage IIIb/IV) nsclc ineligible for RT. Vinorelbine was administered IV on days 1 and 8 of a 21-day treatment cycle, for a total of 6 cycles. The trial was stopped early because of a low enrollment rate after 191 of the 350 targeted patients were randomly assigned between April 1996 and November 1997. Based on 161 evaluable patients, those treated with vinorelbine scored better than control patients on QoL functioning scales, and reported fewer lung cancer-related symptoms but experienced worse toxicity-related symptoms; MST increased from 21 to 28 weeks in the vinorelbine-treated group and the relative hazard of death in this group was 0.65 (JNCI, 6 Jan 1999;91(1):66-72). Vinorelbine has been and is currently being investigated in combination with various chemotherapeutics (Exhibit 6) such as gemcitabine, cisplatin (FO, p 1070), in a triple regimen with either cisplatin and ifosfamide, or with paclitaxel and carboplatin (FO, p 1071), and in multimodality therapies
Market
Worldwide sales were $65 million in 1999

year survival. These results suggest that chemotherapy may have a role in treating nsclc, dispelling the pessimism regarding this form of treatment that originated in poor results from older trials in which in all but the radical RT setting, alkylating agent-based chemotherapy had a detrimental effect which reached conventional significance in the adjuvant surgical comparison (Non-small Cell Lung Cancer Collaborative Group, BMJ, 7 Oct 1995;311 (7010):899-909). However, currently available chemotherapy has done little to improve the outcome of Stage IV disease. MST of patients with Stage IV nsclc, treated with chemotherapy, is only about 3 months longer than that of those managed with best supportive care.

One consideration in using newer agents is cost-benefit issues. Despite their higher cost, however, new agents do not appear to add a significant cost burden to treatment outlays. Cost comparisons of older drugs with newer agents such as paclitaxel, favored the latter approach. In a study performed in Europe by Bristol-Myers Squibb, based on clinical data from a randomized phase III EORTC trial (n=332), variables such as drug acquisition costs, costs of administering the chemotherapy, and costs related to clinical outcomes/complications which differed significantly between treatment arms in the trial, were taken into account to estimate the cost of treatment.

Although the paclitaxel-based regimen was cost-additive in all countries, the extra cost of the chemotherapy was partially compensated by savings attributable to less intensive medical resource use, resulting in a net average incremental cost of $ 2,311 per patient. The clinical trial resulted in a 37% response rate for the paclitaxel arm compared with 26% for teniposide one. The resulting incremental cost-effectiveness of the paclitaxel/ cisplatin combination, if expressed as extra cost per extra responder, was on average $21,009 per responder, which was comparable to the teniposide arm in all countries, except in France, where the former was more cost-effective than the latter (Annemans L, etal, ASCO99, Abs. 1623).

However, an economic analysis of Southwest Oncology Group (SWOG) trial S9509, that compared the currently recommended carboplatin/paclitaxel regimen with a cisplatin/ vinorelbine regimen in the treatment of advanced nsclc, concluded that the former regimen was considerably more expensive in overall costs ($43,826 versus $33,499), mostly attributable to the high drug costs of this combination ($16,735 versus $5,070), that resulted in an overall excess cost of about $12,000. There was no statistically significant difference in survival or cancer-related quality of life between treatment arms, or significant differences in other medical costs (Ramsey SD, ASCO00, Abs. 1913).

Another study, conducted in Spain, compared the cost-effectiveness of gemcitabine/cisplatin versus cisplatin/

etoposide in patients with advanced nsclc using resource utilization data collected in conjunction with the a randomized clinical trial involving 135 chemonaive patients with Stage IIIb/IV, comparing these combinations. There were no differences between both regimens either in terms of survival, or costs (584,523 pesetas for gemcitabine/cisplatin and 589,630 pesetas for cisplatin/etoposide), despite the higher chemotherapy cost of gemcitabine/cisplatin. Savings with gemcitabine/cisplatin were mainly associated with a decrease in hospitalization rate. However, there was a cost-effectiveness advantage in favor of the gemcitabine/cisplatin combination when response rate (40.6%) and time to disease progression (8.7 months) with this regimen that exceeded those associated with cisplatin/etoposide (21.9% and 7.2 months, respectively) were used as endpoints (Sacristan JA, etal, Lung Cancer, May 2000;28(2):97-107).

Types of Chemotherapy in NSCLC

Chemotherapy alone is mostly employed as first-line therapy in advanced disease, and as second-line/salvage therapy in recurrent disease. The gold standard in first-line therapy of advanced disease is a paclitaxel/carboplatin (or cisplatin) combination regimen, but many other chemotherapeutics are routinely used, and/or are being evaluated in clinical trials. In a phase III clinical trial (EORTC-08975), the cispaltin/paclitaxel combination regimen is being compared to the cisplatin/gemcitabine regimen, or paclitaxel/gemcitabine regimen, in chemotherapy-naive patients with Stage IIIb (with malignant pleural effusion, or supraclavicular lymph node involvement) or Stage IV nsclc.

Single-agent chemotherapy is rarely indicated in nsclc although single-agent activity has been observed with such chemotherapeutics as cisplatin, docetaxel, vinorelbine, irinotecan, and topotecan, among others.

In a phase III clinical trial (CLB-9730), being conducted by the Cancer and Leukemia Group B, single-agent paclitaxel is being compared to the standard paclitaxel and carboplatin combination, in chemotherapy-naive patients with advanced (Stage IIIb/IV) nsclc.

Similarly, treatment with single-agent vinorelbine, or gemcitabine, is being compared to a combination of the two drugs in patients aged ≥70 years with Stage IIIb (supraclavicular lymph node metastases, or pleural deposits, not curable with surgery or radical RT) or Stage IV nsclc, in a phase III clinical trial (ITA-MILES, EU-98019, ITA-GOCSI-MILES) being conducted by the Istituto Nazionale per lo Studio e la Cura dei Tumori (Naples, Italy).

Oral topotecan, evaluated in a multicenter phase II clinical trial conducted in the UK, in 30 patients with non-resectable, untreated, advanced nsclc (Stage III/IV), resulted in a 10-month survival rate comparable to that seen with other active agents for this indication. Also the regimen was well tolerated, convenient, and palliative in some patients. Treatment was administered for 5 days, every 21 days. The dose for the first cycle was 2.3 mg/m^2/day and was subsequently modified according to tolerability; dose escalation to 2.7 mg/m^2 for 5 days was possible in 83% of patients. Altogether, 125 cycles were administered. There were 3 (11%) minor responses, and disease stabilized in 10 (37%) patients. MST was 10.2 months. Myelosuppression was the major toxicity with 12 (40%) patients experiencing Grade 3 and 2 (6.6%) Grade 4 neutropenia, and 3 Grade 3 and 1 Grade 4 anemia. There was one episode of Grade 3 thrombocytopenia. The main nonhematologic toxicity was Grade 3 nausea and vomiting in 13% of patients. Regarding disease-related symptoms, 21% of patients reported improvement in dyspnea, 32% in cough, and 29% in fatigue, compared to status at baseline (White SC, etal, ASCO99, Abs. 2033;527a).

Combination chemotherapy is the standard option in advanced/metastatic disease. Two-drug combinations (doublets) involving a variety of agents are being investigated to define doses, timing of administration, maximum effectiveness, and toxicity. In phase II clinical trials, triple combinations (triplets) appear to be achieving similar 1-year survival rates, and overall response rates, to those seen in many doublet combinations with variable toxicity. Phase III clinical trials are attempting to establish the role of triplet regimens in terms of outcome as compared to doublet combinations. For instance, in the treatment of advanced nsclc, the mitomycin/ifosfamide/cisplatin regimen produced a higher response rate without any changes in QoL, and a similar overall survival, time to progression (TTP), and time to treatment failure, as the gemcitabine/cisplatin regimen (Crino L, etal, J Clin Oncol, Nov 1999;17(11):3522-30).

Platinum-based therapy remains the mainstay of treatment for nsclc in combination with other agents. In Europe, the Big Lung Trial (BLT), initiated in November 1995, will enroll 10,000 nsclc patients to assess the benefits of platinum-based chemotherapy in terms of effectiveness, survival, QoL, and cost-effectiveness.

Among doublets are the following combinations (see Exhibit 6):

- paclitaxel plus carboplatin is a moderately active regimen in advanced nsclc (Laohavinij S, etal, Lung Cancer, December 1999;26(3):175-85); paclitaxel administered as a 1-hour infusion, in combination with carboplatin (AUC=7.5), is an active regimen in advanced nsclc (Langer CJ, etal, Eur J Cancer, Jan 2000; 36(2): 183-93)
- gemcitabine and vinorelbine is an active and well-tolerated regimen in patients with advanced nsclc, with response and survival rates at least comparable to those achieved with standard platinum-based regimens (Herbst RS, etal, Semin Oncol, October 1999;26(5 Suppl 16):67-70 and Hainsworth JD, etal, Cancer 15 March 2000;88(6):1353-8); this combination may be particularly suitable for the elderly or for patients who

cannot tolerate more toxic platinum-based regimens (Lilenbaum R, etal, Cancer, 1 February 2000;88(3): 557-62); gemcitabine and vinorelbine should be tested in a triplet combination with a taxane as the third drug, or against a platinum-containing regimen in a phase III study (Isokangas OP, etal, Ann Oncol, Sep 1999;10(9): 1059-63)

- vinorelbine and cisplatin demonstrate substantial activity in terms of objective response and survival, with manageable side-effects in advanced nsclc (Goedhals L, etal, Curr Med Res Opin 1999;15(3):185-92)
- docetaxel and carboplatin is a feasible and well-tolerated outpatient regimen for the treatment of patients with locally advanced and metastatic (Stage IIIb/IV) nsclc (Giannakakis T, Eur J Cancer, 1 April 2000; 36(6): 742-47); a phase II clinical trial (HCRN-007, NCI-V98-1469), evaluating this regimen, is ongoing at Bethany Medical Center (Kansas City, KS)
- docetaxel in full doses, alternating with full doses of other new agents active against nsclc, produced response, toxicity and survival figures that compared favorable with those using concomitant schedules (Mattson K, etal, Anticancer Drugs, January 2000;11(1):7-13)
- gemcitabine plus cisplatin is superior to cisplatin alone as first-line treatment of nsclc, in terms of response rate, time to disease progression, and overall survival (Sandler AB, etal, J Clin Oncol, January 2000;18(1): 122-30); this regimen is associated with a significantly higher response rate than etoposide plus cisplatin, and delays disease progression without impairing QoL in advanced nsclc (Cardenal F, etal, J Clin Oncol, Jan 1999;17(1):12-8)
- intensive IV etoposide and cisplatin demonstrated no benefit but significantly higher toxicity that oral etoposide and cisplatin (Jeremic B, etal, Lung Cancer, September 1999;25(3):207-14)
- CPT-11 in combination with cisplatin is effective in advanced nsclc (Nagao K, etal, Gan To Kagaku Ryoho March 2000;27(3):413-21), and is associated with manageable toxicity (DeVore RF, etal, J Clin Oncol, Sep 1999;17(9):2710-20)
- oral UFT plus cisplatin is a moderately active regimen with an extremely low rate of incidence of myelosuppression as an adverse event (Ichinose Y, etal, Cancer, January 2000: 15;88(2):318-23)
- oxaliplatin plus paclitaxel regimen is being evaluated in a phase II clinical trial (UCCRC-10014, NCI-T99-0008), in Stage IIIb (with pleural effusion) or Stage IV recurrent nsclc, at the University of Chicago Cancer Research Center (Chicago, IL)
- topotecan, administered PO, 5 times daily, in combination with paclitaxel (175 mg/m^2), administered as a 3-hour infusion on day 1, every 21 days, is currently in a phase II clinical trial, being conducted by the Topotecan Study Group, and SmithKline Beecham Pharmaceuticals (Dobbs, TW, etal, ASCO00, Abs. 2049); IV topotecan is also being investigated, in combination with gemcitabine, as second-line therapy of advanced nsclc; both drugs were infused over 30 minutes, with topotecan (0.75 mg/m^2) administered on days 1 through 5, and gemcitabine (400 mg/m^2), on days 1 and 5 only, immediately after topotecan, every 21 days (Rainey JM, etal, ASCO00, Abs. 2032); IV topotecan (0.5 mg/m^2), administered on days 1 to 5, in combination with cisplatin (25 mg/m^2), administered on days 1, 3, and 5, is also being investigated in a phase II clinical trial (Bildat S, etal, ASCO00, Abs. 891)

Among triplet regimens (see Exhibit 6) are the following combinations:

- vinorelbine, cisplatin and ifosfamide is an active combination with a good safety profile when an alternating schedule of cisplatin and ifosfamide is used (Barone C, etal, Oncology 2000;58(1):25-30).
- ifosfamide, carboplatin and etoposide (ICE) is active in locally advanced nsclc with acceptable toxicity, and may also be effective as induction chemotherapy (Scinto AF, etal, Br J Cancer, November 1999; 81(6):1031-6)
- gemcitabine, cisplatin and ifosfamide combination regimen resulted in response rates similar to those obtained with the gemcitabine plus cisplatin with an acceptable toxicity profile (Vandell-Nadal C, etal, Lung Cancer, 1 May 2000: 28(2):109-115)
- mitomycin C, plus cisplatin and etoposide, resulted in response and survival rates comparable with those achieved with standard regimens in advanced nsclc, but was associated with substantial hematologic toxicity, and unacceptable treatment-related mortality (Ali MA, etal, Cancer Invest 2000;18(1):1-5)
- cisplatin combined with carboplatin and vindesine is effective against inoperable nsclc with tolerable toxicities, and a favorable MST (Haneda H, Gan To Kagaku Ryoho, February 2000;27(2):227-31)
- carboplatin, docetaxel, and gemcitabine regimen is effective for the treatment of chemotherapy-naive patients with advanced nsclc, causing only moderate toxicity (Pectasides D, etal, J Clin Oncol, Dec 1999; 17(12):3816-21)
- gemcitabine, paclitaxel and cisplatin regimen in treatment-naive, advanced nsclc appears safe and exhibits noteworthy activity both in terms of response rate, time to progression, and survival (Sorensen JB, etal, Ann Oncol, September 1999;10(9):1043-9)
- carboplatin, paclitaxel, and Herceptin regimen is being evaluated by ECOG in a phase II clinical trial (E-2598) in Stage IIIb (with pleural or pericardial effusion), or Stage IV nsclc

Triplet combinations, adding either vinorelbine or paclitaxel to a combination of a high-dose regimen of cisplatin (100 mg/m^2) and gemcitabine (1 g/m^2), administered on days on days 1, 8, and 15, at 4-week intervals, proved to be more effective than the two-drug regimen without significantly increased toxicity. In the triplet combinations, the cisplatin dose, administered on days 1 and 8, was lowered to 50 mg/m^2, and gemcitabine administration was limited to days 1 and 8 with day 15 omitted. In the gemcitabine, cisplatin and vinorelbine combination, vinorelbine (25 mg/m^2) was administered on days 1 and 8, and, in the gemcitabine, cisplatin and paclitaxel combination, paclitaxel (125 mg/m^2) was also administered on days 1 and 8.

Among 360 patients, equally randomized between the three regimens, Grade 3/4 toxicities, namely anemia, peripheral neuropathy, and fatigue in the paclitaxel combination, were somewhat higher with the triplet regimens, but nausea and vomiting was significantly higher (30% versus 15% and 18%) with the doublet regimen. MST was 51 weeks for either triplet regimen, compared to 38 weeks for the gemcitabine/cisplatin combination, and the 1-year survival was 39%, 47%, and 46%, respectively. Median TTP was 19 weeks for the doublet regimen, 24 weeks for the vinorelbine-based triplet, and 29 weeks for the paclitaxel one. Overall survival in Stage IV disease was 31%, 49%, and 50%, respectively, and ORR was 31% (0% CR), 53% (4% CR) and 58% (53% CR), respectively (Comella G, etal, ASCO00, Abs. 1933). The Southern Italian Cooperative Oncology Group (SICGO), that conducted this trial, is planning a 4-arm phase III randomized clinical trial to compare these triplets with the non-cisplatin doublets of gemcitabine and vinorelbine, or gemcitabine and paclitaxel.

High-dose chemotherapy (HDC) is a controversial treatment approach in advanced cancer. A dose-intensive 4-drug combination regimen involving ifosfamide, carboplatin, etoposide, and paclitaxel (ICE-T), was evaluated in a phase II clinical trial in 41 patients with advanced nsclc (Stage IIIb=32% and Stage IV=68%). The regimen was based in a phase I study, that demonstrated that, with G-CSF support, full-dose, single-agent paclitaxel by 24-hour infusion can be safely administered with full dose ICE chemotherapy in advanced lung cancer. While toxicity was manageable, the effectiveness of this intensive combination chemotherapy measured by response rate and survival, was disappointing, leading to the conclusion that dose-intensive, multiagent chemotherapy regimens do not provide a therapeutic advantage over less intensive protocols in advanced nsclc (Strauss GM, etal, ASCO99, Abs. 1855:481a).

HDC with autologous peripheral stem cell transplantation and G-CSF, is currently being evaluated in Stage IIIb/IV nsclc, in a phase II clinical trial (CPMC-IRB-7836, NCI-G98-1408, CU-CAMP-017), being conducted at Herbert Irving Comprehensive Cancer Center (New York, NY).

Novel Chemotherapeutics Approved for the Treatment of NSCLC

Newly introduced chemotherapeutics for the treatment of nsclc are described in Exhibit 5. Also, numerous agents are in various stages of development. According to NEW MEDICINE's Oncology KnowledgeBASE (nm/OK; oncology-knowledgebase.com), as of early 2000, there were 262 agents in all phases of development that may be applicable to the treatment of lung cancer, and 52 agents in development specifically targeting nsclc. Novel agents in development are the topic of Part VI of this series on lung cancer.

BIOLOGIC AGENTS

Biologic agents such as growth factors are used in nsclc to support treatment with new promising drug combinations including vinorelbine, gemcitabine, paclitaxel, or docetaxel, that are often highly toxic in full doses. However, outside controlled clinical trials, the role of growth factors in the treatment of nsclc should be within American Society of Clinical Oncology (ASCO) guidelines (Gridelli C, etal, Clin Ter, May-Jun 1999;150(3):231-4). Biologic agents also exhibit antitumor activity in many cancer types including nsclc. Interleukin-2 (IL-2) and interferon β (IFN-β), exhibited antitumor activity in preclinical models of nsclc, and are currently in clinical trials alone, or in combination, in the treatment of nsclc.

Interleukin-2 (IL-2)

In a randomized phase II clinical trial (ECOG PZ586), conducted at the Albert Einstein Cancer Center (Philadelphia, PA), 76 patients with Stage IV nsclc were administered IL-2 (Proleukin; Chiron) (6 x 10^6 units/m^2) thrice weekly, or the combination of IL-2 (5 x 106 units/m^2), and IFN-β (6 x 10^6 units/m^2), both administered thrice weekly as an IV bolus injection on an outpatient basis. Objective responses were observed in 3/76 (4%) patients. Grade 4 toxicity occurred in 3/39 patients treated with IL-2 alone, and in 4/37 patients treated with IL-2 and IFN-β. An additional lethal respiratory toxicity occurred in a patient treated with IL-2 and IFN-β. MST of all patients was 33 weeks. Despite the low response rate, IL-2 appears to have a favorable impact on survival comparable to chemotherapy (Tester WJ, etal, Lung Cancer, Sep 1999;25(3):199-206).

In a clinical trial conducted at the University of Mainz, in Germany, inhaled IL-2 was effective in some patients with lung metastases associated with malignant melanoma, that occur in as many as 50% of patients with Stage IV disease. High-dose IL-2 (36 million IU) was delivered by inhalation 6 days each week, for up to 6 months, to 27 patients who had progressive malignant melanoma despite chemotherapy. There were 5/27 (18.5%) CR and 8/27 (29.6%) PR while disease stabilized in 5, and progressed in 8. CR persisted for a median 12 months, whereas disease progressed in the lungs within 6 months in nearly 80% (10/13) of those in PR or SD. The only treatment-

related side effects were slight fever in 2/27 patients, and cough in 23/27 (Enk AH, etal, Cancer 2000;88:2042-2046).

Interferon β (IFN-β)

IFN-β has demonstrated a variety of antitumor activity in nsclc *in vitro*, and various forms of IFN-β are in clinical trials. *In vitro*, it was shown that IFN-β induces NCI-H596 cells to enter multiple cell death pathways that are differentiation related (Zhang H, etal, Exp Cell Res, 25 Feb 1999;247(1):133-41). Also, both natural and recombinant IFN-β were shown to exert an enhancing effect on radiation damage in tumor cells *in vitro* and may, therefore, act as radiosensitizers. Interestingly, these agents appear to simultaneously exert a radioprotective effect on normal lung tissue.

Impaired radiation repair, or accumulation of sublethal damage associated with IFN-β exposure, may play a role for the radiosensitizing effect of natural IFN-β (nIFN-β). When the combined effect of nIFN-β and ionizing radiation was tested *in vitro* on 5 different tumor cell lines, and 1 embryonal lung fibroblast cell line, the maximum sensitizing enhancement ratio (SER) at the 37% survival level was seen in the A549 lung cancer cell line. In all cases nIFN-β enhanced the effect of radiation in this tumor cell line, but not in nonmalignant lung fibroblasts (Schmidberger H, etal, Int J Radiat Oncol Biol Phys, 15 Jan 1999;43(2):405-12). In a comparison of the radiosensitizing effect of natural IFN-β (Fiblaferon; biosyn), recombinant IFN-β1a, and recombinamt IFN-β1b (Betaferon; Schering), in the A549 lung-cancer cell line, all three types of IFN-β enhanced the radiation sensitivity of A549 cells in a similar way, but the isoeffective concentration of rIFN-β1b was 2.7-fold higher than that of rIFN-β1a or nIFN-β (Schmidberger H, etal, J Cancer Res Clin Oncol 1999;125(6):350-6).

Several versions of IFN-β are in late-stage clinical trials in various cancers including nsclc. In a phase II clinical trial, conducted between February 1994 and November 1996 at Zentralkrankenhauses Sankt-Jurgen-Strasse (Bremen, Germany), 14 patients with Stage IIIb nsclc were treated with locoregional radiation (up to 59.4 Gy), with daily doses of 1.8 Gy, and 5 fractions per week. Fiblaferon (5 million units) was administered IV, immediately preceding RT, on the first 3 days of weeks 1, 3 and 5. There were 4/14 (28.6%) CR and 7/14 (50%) PR, for an ORR of 78.6%. After a mean follow-up time of 23.3 months the 1-, 2- and 3-year survival rates were 56.3%, 37.5% and 37.5%, respectively; MST was 13 months. Regarding toxicity, 3/14 (21.4%) patients experienced 7 Grade 3 acute side effects and 2 (14.3%) from 1 Grade 3 late toxicity in each case. One patient, whose right lung was resected 3 months after completion of RT, developed two Grade 4 complications (Bund J, etal, Strahlenther Onkol, Jun 1998;174(6):300-5).

Serono's (Geneva, Switzerland and Norwell, MA) Rebif, a natural, fibroblast-derived IFN-β, is currently in phase III clinical trials in nsclc.

MULTIMODALITY THERAPY

Multimodality therapy is becoming the treatment of choice in early, and locally advanced disease. Despite the success of surgery in curing very early nsclc, locally advanced nsclc is considered a systemic disease that requires a multimodality approach for optimal intervention (Rosell R and Felip E, Semin Surg Oncol, Mar 2000;18(2):143-51). Multimodality approaches now in favor involve preoperative (neoadjuvant or induction) chemotherapy, an established treatment for resectable Stage IIIa nsclc, and concurrent chemotherapy and RT for locally advanced, unresectable nsclc. In randomized trials and meta-analyses, concurrent, platinum-based chemoradiotherapy was shown to offer a distinct survival benefit when compared to RT alone, in treating inoperable Stage III nsclc.

Based on the meta-analysis of records of 9,387 patients treated for nsclc, described above (Non-small Cell Lung Cancer Collaborative Group, BMJ, *ibid*), benefits were greatest for patients with locally advanced disease treated with chemoradiotherapy, resulting in 4% more patients being alive at 2 years, and 2% more patients being alive at 5 years. In early stage disease, addition of cisplatin-based chemotherapy to surgery alone, or to surgery plus RT, resulted in absolute survival increases of 2% to 3% at 2 years, and 2% to 5%, at 5 years. Trials comparing surgery with surgery plus chemotherapy, and radical RT alone, with radical RT plus chemotherapy, produced a hazard ratio of 0.87 with a 13% reduction in the risk of death, equivalent to an absolute benefit of 5% at 5 years, in the former, and 4% at 2 years, in the latter.

Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended in incompletely resected nsclc when presence of residual tumor in the resection margin, or presence of metastasis in the highest paratracheal lymph node sampled during protocol-directed surgical staging of the mediastinum, is detected. Chemotherapy is also being evaluated in conjunction with RT in nonresectable early-stage nsclc.

Among 1,173 patients treated surgically between 1980 and 1997 at the Lithuanian Oncology Center (Vilnius, Lithuania), 42 patients (T1N0=12, T2N0=11, T2N1=7, N2=12; SCC=19, adenocarcinoma=13, sclc=9, and other=1) were treated with a limited resection with lymph-node dissection. Postsurgery, 9 patients were treated with RT, and 9 with chemotherapy. Best follow-up results, with a median survival of 45.7 months, were observed in patients with T1/2N0 disease who were also administered adjuvant therapy. Median survival of those treated by surgery alone was 36.7 months, and was only 9 months in those with N2 disease. These results indicate that limited resection with lymph nodes dissection can be performed only in T1/2N0 disease. In the case of N0 undifferentiated carcinoma (anaplastic, small cell) adjuvant therapy must be administered postoperatively while in N1 or N2 disease

adjuvant therapy is recommended regardless of tumor histology (Jackevicius A, etal, Acta Chir Hung 1999; 38(1): 49-51).

In a phase III clinical trial, 172 patients were randomized to either postoperative RT alone, or postoperative RT plus chemotherapy, with a 6-month regimen of cyclophosphamide, doxorubicin and cisplatin. Among 164 patients eligible for analysis at a mean time since randomization of 3.7 years, those treated with chemotherapy showed significantly longer RFS which held true in nonsquamous cancer cases, and approached significance in SCC cases. There was a 14% difference in survival rate favoring the chemotherapy arm 1 year after randomization. Analysis of sites of recurrence showed a significant decrease in distant metastases in the chemotherapy arm. MST for the entire group was approximately 17 months, and 35% were alive 2 years after resection. Toxicity of treatment consisted of mild-to-moderate esophagitis, and hematologic, gastrointestinal, and skin toxicity (Lung Cancer Study Group, J Clin Oncol, Jan 1988;6(1):9-17).

The role of adjuvant chemotherapy based on a paclitaxel plus carboplatin regimen, is being evaluated by the Cancer and Leukemia Group B and Radiation Therapy Oncology Group, in a phase III clinical trial (CLB-9633) in chemoradiotherapy-naive patients with Stage Ib (T2N0) nsclc.

Chemoradiotherapy

Chemoradiotherapy is becoming an important treatment approach in locally advanced (Stage III) nsclc (Exhibit 6). According to preliminary results from a multicenter clinical trial of 611 newly diagnosed patients with locally advanced nsclc, enrolled in 3 different arms, concurrent therapy with cisplatin and vinblatine plus concurrent RT, or cisplatin and oral vepesid with concurrent RT produced quite promising survival outcomes than a similar chemotherapy regimen with sequential RT (Curran WJ, etal, ASCO00, Abs. 1891). In one trial, patients treated with a docetaxel/cisplatin combination and RT, experienced a very high response rate while toxicity was manageable (Nyman J, etal, ASCO99, Abs. 1998:518a). In another trial that compared concurrent with sequential thoracic RT in combination with MVP chemotherapy consisting of mitomycin, cisplatin and vepesid, concurrent RT with MVP resulted in a significant advantage in survival (Furuse K, etal, ASCO99, Abs. 1770:458a). Treatment consisting of induction chemotherapy with cisplatin and CPT-11, followed by RT and CPT-11, also proved feasible, indicating that irinotecan may be a promising radiation sensitizer in the management of locally advanced nsclc (Yamamoto N, etal, ASCO00, Abs. 1953).

Chemoradiotherapy appears to be particularly effective in patients with supraclavicular (SN) metastases. When those with SN+ were treated with chemoradiotherapy, their overall survival, progression-free survival (PFS), and metastases-free survival (MFS) was similar to those without SN metastases. Among 256 Stage IIIb patients (SN+=47 and SN-=209) treated, MST was 16.2 months, and 15.6 months, for SN+ and SN- patients, respectively, and the 4-year actuarial survival rates were 21% and 16% for SN+ and SN- patients, respectively. There was no statistically significant difference in the 4-year PFS rates (19% versus 14%) and no clinically significant differences in toxicity (Machtay M, etal, Int J Radiat Oncol Biol Phys,1 Jul 1999;44(4):847-53).

Neoadjuvant/Induction Chemotherapy and Trimodality Therapy

Numerous phase I/II clinical trials evaluating induction chemotherapy, are ongoing. Neoadjuvant chemotherapy is increasingly used to enable/optimize resection in patients presenting with locally advanced nsclc. For instance, clearance of viable tumor cells in mediastinal lymph nodes (MLN) by induction chemotherapy, referred to as MLN downstaging, plays an important role in the treatment of N2 nsclc. Because reassessment of mediastinal lymph nodes after induction chemotherapy by CT is far from accurate, and a second mediastinoscopy is often technically difficult, investigators used FDG-PET in the initial staging of N2 disease, and in staging after induction chemotherapy. Among 15 surgically staged nsclc patients with N2 disease, after three cycles of platinum-based IC, a second PET was performed before locoregional therapy, consisting of either surgery (n=9) or RT (n=6). PET was 100% accurate in predicting MLN downstaging (true negatives=6, and true positives=3), while CT was only 67% accurate (false positives=2, and false negatives=1). Survival was significantly better in patients with mediastinal clearance, or with a greater than 50% decrease in the standardized uptake value (SUV) of the primary tumor after chemotherapy (Vansteenkiste JF, etal, Ann Oncol, Nov 1998;9(11):1193-8).

A phase III clinical trial (MRC-LU22, EU-97016), being conducted in the UK by Medical Research Council (MRC) Clinical Trials Unit (London, UK), is comparing surgery alone, or with neoadjuvant chemotherapy, in nsclc patients with no previous therapy. Neoadjuvant chemotherapy consists of a triplet IV regimen of either mitomycin, vinblastine, and cisplatin, or mitomycin, ifosfamide, and cisplatin.

Trimodality therapy involving chemotherapy followed by twice-daily RT with concomittant low-dose chemotherapy, and subsequent surgery, is also being attempted in locally advanced nsclc. A phase I/II clinical trial (NU-99L1, NCI-G99-1585) employing a complex trimodality induction regimen consisting of a combination of 4 chemotherapeutics, i.e., carboplatin, gemcitabine, paclitaxel, and vinorelbine, and RT, and surgery when feasible, is ongoing at Robert H. Lurie Comprehensive Cancer Center, at Northwestern University (Chicago, IL).

Exhibit 6
Phase II and III Combination and Multimodality Clinical Trials in NSCLC

Protocol	Phase➢Location ❑ Population and Indication ❑ Location ❑ Reference	Toxicity	Results
Multimodality Therapy			
Treatment consisted of 3 cycles of cisplatin (20 mg/m²), on days1-5, and 5-FU (500 mg/m²), on days 1-5, *q* 4 weeks, and concurrent hyperfractionated thoracic radiation (1.25 Gy) *bid*, with a 6-hour interfraction interval (total radiation dose was 62.5-70 Gy)	Phase II (b1/94; c11/96)➢ Japan ❑ 50 previously untreated patients with locally advanced unresectable Stage IIIa (N2) or Stage IIIb nsclc ❑ National Shikoku Cancer Center Hospital (Matsuyama, Japan) ❑ Segawa Y, etal, Br J Cancer, Jan 2000;82(1):104-11	Major toxicities were ≥ Grade 3 leukopenia (58%) and neutropenia (60%); other ≥ Grade 3 toxicities included thrombocytopenia (26%), anemia (26%), nausea/vomiting (16%) and radiation esophagitis (6%); there was one treatment-related death	ORR was 74% (37/50 patients) with a CR rate of 4% (2/50); within a median follow-up time of 41.0 months, 35/50 patients had died; median time to progression for responding patients was 14.1 months (range=2.6-51.3+ months); MST was 18.7 months; 1-, 2- and 3-year survival rate, was 66.0%, 46.0%, and 27.6%, respectively; survival outcome was strongly affected by the extent of nodal involvement (MST was 27.4 months for N0/2 disease (n=37) versus 10.7 months for N3 disease (n = 13)
Patients were randomized to either 4 cycles of cisplatin (60 mg/m²) on day 1, and etoposide (120 mg/m²), on days 1-3, administered concurrently with RT (5040 cGy) in 28 daily 180 cGy fractions, or RT alone, at this same dose; 66% (121/183) of patients in the chemoradiotherapy arm were treated with all 4 cycles of chemotherapy, while 76% (139/183) were treated with RT only; in the RT arm only, 83% (139/168) of patients were treated with the requisite RT dose	Phase III (c2/97)➢USA (ECOG:E3590) ❑ 488 patients with Stage II and Stage III nsclc, recruited between April 1991 and February 1997, who had undergone complete resection of the primary tumor, and a thorough mediastinal lymph node sampling or dissection ❑ multicenter ❑ Keller SM, etal; ASCO99, Abs 1793:465a	Grade 3/4 toxicity consisting largely of leukopenia (8.8%) and esophagitis (1.3%) in patients treated with RT only, and 25% and 65% in those treated by chemoradiotherapy; treatment-associated mortality was 2.2% in the chemoradiotherapy arm, and 2.4% in the RT arm	351 patients were eligible for analysis with a median follow-up of 37 months; at 40.5 months follow-up, MST of patients randomized to RT only was 38.2 months, and to chemoradiotherapy 37.6 months; 5-year survival was projected at 39% in the RT arm, and 33% in the combined arm; there was no statistically significant survival advantage for either treatment arm; MST in N1 and N2 disease was 45.2 months and 30.6 months, respectively
Carboplatin (400 mg/m²) IV on days 1-21 + etoposide (50 mg/m²) PO on days 1-21 and 29-42 plus accelerated hyperfractionated RT starting on day 1, with a total dose of 51 Gy in 34 fractions over 3.5 weeks	Phase II (b1/88; c6/93)➢ Yugoslavia ❑ 58 patients with Stage III nsclc ❑ University Hospital (Kragujerac, Yugoslavia) ❑ Jeremic B, etal, Int J Radiat Oncol Biol Phys, 1 May 1999;44(2):343-348	Grade 3 or 4 hematologic, esophageal, and bronchopulmonary acute toxicities were observed in 22%, 7%, and 4% of patients, respectively; no Grade 5 or late grade ≥3 toxicities occurred	In 55 evaluable patients, the ORR was 65% and CR rate was 27%; MST was 10 months, and the 1-, 2-, and 5-year survival rate was 45%, 24%, and 9.1%, respectively; median time to relapse was 8 months, and the 1-, 2-, and 5-year RFS rate was 45%, 20%, and 9.1%, respectively; median time to local recurrence was 14 months, and the 5-year local control rate was 13%; median time to distant metastasis was 18 months, and the 5-year distant metastasis-free rate was 15%

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Patients were treated with 3 courses of docetaxel (75 mg/m^2)and cisplatin 75 (mg/m^2), on day,1 with premedication of steroids for 3 days; the third course was administered concomitantly with RT; total RTdose was 64.6 Gy with two daily fractions of 1.7 Gy (>6-hour interval); one week split was introduced after 40.8 Gy, making the treatment time 4.5 weeks; a CT scan was used to evaluate response after 2 cycles of chemotherapy, and after 3 months to evaluate the combined treatment	Phase II (b12/96,c10/98)➢ Sweden ❑ 20 consecutive patients (SCC=55%, adenocarcinoma=40% and large-cell carcinoma=5%) with locally advanced (Stage IIIa=4 and IIIb=20), unresectable nsclc (pretreatment weight-loss was >5% in 40%) ❑ Gothenburg University (Gothenburg, Sweden) ❑ Nyman J, etal, ASCO99, Abs. 1998:518a	A total of 57 cycles were administered; Grade 3/4 neutropenia was seen in 45%, febrile neutropenia in 12%, and thrombocytopenia in 2%; there was no included Grade 2/3 asthenia anemia; nonhematologic toxicities (51%), fluid retention (2%), and diarrhea (12%); there was no neuropathy; Grade III esophagitis was seen in one patient (6%) and Grade II in 12 (67%); one patient died of pneumonitis 3 months after completion of treatment; there were 2 patients with Grade II pneumonitis	After 2 cycles of chemotherapy 13 patients achieved PR, and 6 SD; ORR was 65% (13/20); 3 months after RT there were 13 PR, 1 SD, 1 PD and 1 NE; ORR was 81% (13/16); MST had not been reached at the longest follow-up of 21 months; 8 patients died, 5 of lung cancer
Patients were randomized to either concurrent or sequential thoracic RT in combination MVP chemotherapy consisting of mitomycin (8 mg/m^2) and cisplatin (80 mg/m^2) on days 1 and 29, and vindesine (3 mg/m^2) on days 1, 8, 29 and 36; thoracic RT (2 Gy/fraction for 14 times or 28 Gy) was administered beginning on day 2 of MVP, for 3 weeks, and after a rest period of 10 days, 28 Gy were administered for another 3 weeks, or RT (56 Gy), administered as a conventional schedule, starting after completion of MVP; patients responding to chemotherapy in the sequential arm, were administered 1 or 2 cycles of chemotherapy after completion of RT	Phase III (b8/92; c12/94)➢ Japan ❑ 320 patients with unresectable Stage III nsclc, including cases of supraclavicular lymph node metastases but excluding T3N0M0 cases, and those involving pleural effusion ❑ Osaka Central Hospital (Osaka, Japan) for the West Japan Lung Cancer Group ❑ Furuse K, etal, ASCO99, Abs. 1770:458a, and Furuse K, etal, J Clin Oncol, Sep 1999; 17(9):2692-9	Among 314/320 patients evaluable for Grade III/IV toxicity, there was one toxic death from sepsisin the concurrent radiation, and MVP group and 2 patients died from radiation radiation group; other toxicities included neu-tropenia, 94.2% and 73.4%, respectively, and anemia, 48.7% and 31.8%, respectively (Furuse K, etal, ASCO97, Abs. 1649:459a)	Among 314/320 patients evaluable for response, at a 5-year median follow-up, survival favored concurrent therapy over sequential therapy, 64.1% versus 54.8% at 1 year, 34.6% versus 27.4% at 2 years, 22.3% versus 14.7% at 2 years, 16.9% versus 10.1% at 2 years, and 15.8% versus 8.9% at 5 years; in addition, MST of 16.5 months and 13.3 months, respectively, also favored concurrent over sequential therapy; beyond 4 years, there were 11 survivors in the concurrent therapy versus 7 in the sequential therapy group
Patients were administered vinorelbine (25 mg/m^2), on days 1 and 8, ifosfamide (3 g/m^2), on day 1 (with mesna), and cisplatin (80 mg/m^2), on day 1 every 3 weeks (VIP regimen); 18/22 patients with objective response or SD, eligible for thoracic RT, were treated with standard fractionation (200 cGy/day, 5 fractions/wk/6 wk) RT, that was started from 4 to 6 weeks after the end of chemotherapy	Phase II➢Italy ❑ 28 patients with Stage IIIb nsclc ❑ Unita Operativa di Oncologia Medica (Pisa, Italy) ❑ Baldini E, etal, Semin Oncol, Feb 2000; 27(1 Suppl 1):28-32	The most relevant acute and late toxicities of RT were Grade3 dysphagia and pneumonitis in 2 patients; Grade 3 lung fibrosis occurred in 6 patients; curative thoracic RT was well tolerated after VIP induction chemotherapy	26/28 patients were treated with at least 3 courses of induction chemotherapy and were evaluable for response which was seen in 15/26 (58%); CR rate was 4% (1/26), PR rate was 54% (14/26), and disease stabilized in 7 and progressed in 4 during chemotherapy; 14 completed RT treatment, reaching a total dose of 60 Gy; there were 6 clinical remissions, and disease stabilized in 3 and progressed locally in 5 after RT; median PFS for 18 patients treated with RT was 14 months (range=4 to 36 months), and overall survival was 26 months; the 1- and 2-year survival rates were 61% and 52%, respectively; the first site of recurrence was local in 10/18 (56%) patients and distant in seven (38.8%), and both local and distant in 1 patient

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UFT (400 mg/m^2) was administered orally on days 1 to 52, and cisplatin (80 mg/m^2) IV, on day 8; 29 and 50; a total dose of 60.8 Gy of RT was delivered in 38 fractions on days 1 to 52	Phase II➢Japan ❑ 17 previously untreated patients with unresectable Stage III nsclc ❑ National Kyushu Cancer Center (Fukuoka, Japan) ❑ Ichinose Y, etal, Oncology (Huntingt), Jul 1999;13(7 Suppl 3):98-101	Hematologic toxicity was moderate; Grade 3 leukopenia occurred in 10 (59%) patients, there was no Grade 4 hematologic toxicity or Grade 3/4 nonhematologic toxicities	16/17 experienced PR (94%); median time to tumor progression was 30 weeks (range=8 to 87 weeks); the 1-year survival rate was 80%
Treatment consisted of cisplatin (80 mg/m^2), administered on days 1 and 29, CPT-11 (60 mg/m^2), administered pre-RT, on days 1, 8, 15, 29, 36, 43, and irinotecan (30 mg/m^2) administered post-RT, on days 57, 64, 71, 78, 85, 92; thoracic RT (2 Gy/day for a total of 60 Gy) was administered on day 57	Phase II (b2/98; c1/99)➢ Japan ❑ 68 patients with locally advanced (Stage IIIa=28 and Stage IIIb=46; SCC=32, adenocarcinoma=32 and other=4) inoperable nsclc ❑ Kinki University, School of Medicine (Osaka, Japan) ❑ Yamamoto N, etal, ASCO00, Abs. 1953	Grade 3/4 toxicities during induction chemotherapy consisted primarily of neutropenia (41%/31%), and diarrhea (14%/5%); Grade 3/4 toxicities during concomitant RT and CPT-11 consisted of neutropenia (10%/6%), esophagistis (4%/0%), and hypoxia (4%/2%); there were no treatment related deaths	ORR was 63.3%, consisting of 5.9% CR, and 57.4% PR; MST had not been reached; 1-year survival rate was 71.7%
Neoadjuvant Chemotherapy			
Docetaxel (85 mg/m^2), on day 1,plus cisplatin (40 mg/m^2), on days 1 and 2, administered preoperatively, 3 times, at 3-week intervals; those with PR, CR, or SD, underwent radical resection including mediastinal lymphadenectomy; postoperative RT was administered if the resection was not complete and/or the first mediastinal lymph node was involved	Phase II➢Switzerland ❑ 34 patients with Stage IIIa (N2) nsclc ❑ Inselspital and Tiefenau Hospital (Bern, Switzerland), for the Swiss Group for Clinical Cancer Research ❑ Betticher DC, etal, ASCO99, Abs. 1824:473a	Grade 3 toxicity that involved diarrhea, paresthesia, pneumonia, and fatigue, occurred in 4 cycles/patients; there was one fatality from gastric bleeding; Grade 3/4 hematologic toxicity involved granulocytopenia	ORR among 32 evaluable patients was 21/32 (66%), with 4/32 (12%) CR and 17/32 PR (53%); disease stabilized in 30% and progressed in 6%; down-staging with negative first mediastinal lymph node at surgery occurred in 60% of patients and complete resection was possiblein 70%; there were no postoperative pulmonary complications but one patient died from a heart attack on day 4 after surgery
Paclitaxel (200 mg/m^2) was administered for 3 courses as a 3-hour infusion with premedication, followed by carboplatin (AUC=6); patients were also registered for the ongoing EORTC 08941 trial comparing surgical resection with radical RT after chemotherapy	Phase II (b3/97, c 9/98)➢ Belgium ❑ 57 chemotherapy- and RT-naïve patients with pathologically confirmed, mediastinoscopy-proven Stage IIIa/N2 nsclc ❑ EORTC (Brussels, Belgium) ❑ O'Brien MER, etal, ASCO99, Abs. 1898:?	Grade 3/4 toxicity was exclusively hematologic with leukopenia (2%), neutropenia (52%), and anemia (2%), and 1 (2%) case of neutropenic fever; Grade 3 toxicity was lethargy (9%), sensory neuropathy (5%), and one case (2%) each of motor neuropathy, anorexia, nausea, vomiting, skin toxicity, nausea, arthalgia, and myalgia; Grade 2/3 alopecia occurred in 52% and 35% of patients, receptively	Among 40 evaluable patients for response and 43 for toxicity, the objective rate was 59%
Patients were treated perioperatively with paclitaxel (225 mg/m^2) as a 3-hour infusion, and carboplatin (AUC=6), administered every 21 days, for two cycles before, and three cycles after surgery, in those who underwent complete resection	Phase II (b6/97, c7/98)➢USA ❑ 94 patients with clinical Stage T2N0 (n=45), T1N1 (n=1), T2N1 (n=26), T3N0 (n=17), T3N1 (n=5) nsclc ❑ Biomodality Lung Oncology Team (BLOT), M. D. Anderson Cancer Center (Houston, TX) ❑ Pisters KMW, etal, ASCO99, Abs. 1800:467a	No increased or unexpected toxicity was observed	Of the 92 patients with resectable disease, 83 (90%) were explored and 75 (82%) were completely resected; CR = 4%; there were 3 deaths, one during induction chemotherapy and 2 postoperatively

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26 patients (Stage Ib=10; Stage II=16) in the neoadjuvant groupwere treated with paclitaxel (200 mg/m^2) and carboplatin (AUC=6), every 3 weeks, for 3 cycles, and 23 patients (Stage Ib=8; Stage II=15) in the adjuvant group were treated with the same regimen for 3 cycles; patients with Stage II nsclc in the neoadjuvant group, were also treated with thoracic RT and postoperative weekly paclitaxel (50 mg/m^2) and carboplatin (AUC=2) for 6 weeks; those with Stage II disease in the adjuvant group were also treated with RT and weekly chemotherapy after the initial 3 cycles of chemotherapy	Phase II➢USA ❑ 71 patients with clinical Stage Ib or II nsclc ❑ Sarah Cannon Cancer Center (Nashville, TN), Graves Gilbert Clinic (Bowling Green, KY), Consultants in Blood Disorders and Cancer (Louisville, KY), and Louisiana Oncology Associates (Lafayette, LA) for the Minnie Pearl Cancer Research Network ❑ Greco, FA, etal, ASCO99, Abs. 1952:506a	This combined modality regimen in either the neoadjuvant or adjuvant settings is feasible and relatively safe in the treatment of early stage nsclc; 3 cycles of this regimen were relatively well tolerated; combined RT and weekly chemotherapy was administered to 90% of eligible patients (60% as scheduled); among 49 patients [Stage Ib=18, Stage II=31 (IIA=7; IIB=24)] with (n=17), large cell cancer (n=7), adenocarcinoma (n=18), SCC evaluable patients, there were and mixed cancer (n=7), fully Grade 3/4 esophagitis was the no treatment-related deaths; most common toxicity (25%); severe lung toxicity occurred in only one patient	All 3 cycles of either neoadjuvant (24/26) or adjuvant (22/23) chemotherapy were completed by 46/49 patients; 17/23 patients in the adjuvant chemotherapy group remained progression-free, and 6 relapsed, at a median follow-up of 14 months; 9 (Stage Ib=4, IIb=4, IIa=1)/26 patients in the neoadjuvant group, who were medically inoperable at diagnosis were treated first with adjuvant chemotherapy, and then with thoracic RT (60 Gy) concurrently with weekly paclitaxel (50 mg/m^2) and carboplatin (AUC=2), for 6 weeks; although 17/26 patients in the neoadjuvant group were candidates for resection at the time of diagnosis, 5 did not have surgery; among the 12 patients whose tumors were resected there were 2 CR (16.7%), 9 PR (75%) and disease stabilized in 1 (.08%); 10 remained progression free at 8+ months and 26+ months, and 2 progressed/died at 4 months and 11 months; tumors progressed in 11/31 patients with Stage II nsclc, and in 5/18 patients with Stage Ib nsclc (neoadjuvant=10 and adjuvant=6)
Induction regimen consisting of 4 doses of cisplatin (100 mg/m2), 7 doses of vinblastine, and 2 doses of mitomycin, administered over 9 weeks; patients were subsequently treated either with surgery or RT	Phase II (c6/99)➢USA ❑ 37 patients with Stage III nsclc (Stage IIIa=26 and Stage IIIb=11) enrolled between October 1992 and March 1996 ❑ Memorial Sloan-Kettering Cancer Center, Cornell U Medical College (New York, NY) ❑ Ng KK, etal, Cancer, 1 Oct 1999;86(7):1189-97	Myelosuppression was the most common side effect; there were no treatment-related deaths	ORR was 65% with a complete resection rate of 67%; MST was 17 months, with 66% of patients alive at 1 year; complete resection and Stage IIIa involvement were favorable prognostic indicators for survival; no Stage IIIb patients underwent a complete resection
Patients were randomized to either surgery alone (arm 1=186) or surgery with neoadjuvant MIP chemotherapy (arm 2=187) which consisted of two cycles of mitomycin (6 mg/m^2) ifosfamide (1.5 g/m^2) and cisplatin (30 mg/m^2), administered at a 3-week interval; 2 more cycles were administered postoperatively to those with objective responses; in both arms, patients with Stage IIIa disease were administered postoperative thoracic RT; among the 355 responding patients (Stage I/II=188 and Stage IIIa=167), surgery was performed in 174 in arm 1 and 169 in arm 2; RT was delivered to 72 patients in arm 1, and 41 in arm 2	Phase III (b7/91, c9/98)➢ France ❑ 373 patients with Stage I (except T1N0), Stage II and Stage IIIa unresectable nsclc ❑ French Thoracic Cooperative Group (Besançon, France) ❑ Depierre A, etal, ASCO99, Abs. 1792:465a	Perioperative toxicity was high; an important contributor to the high early toxicity associated with the MIP regimen is probably mitomycin C that leads to frequent postoperative pulmonary complications with a mortality rate ranging between 5% to 15%; non significant excess of deaths occurred during the treatment period, especially by bronchopleural fistula (n=6)	CR was 11% (19/174) and PR was 53% (95/174); in arm 1 MST was 26 months with 1-, 2- and 3-year survival rates at 73%, 52% and 41%, respectively; in arm 2 MST was 36 months with 1-, 2-, and 3-year survival rates at 77%, 59% and 49%, respectively; neoadjuvant chemotherapy after 150 days, significantly favored survival (RR=0.71) but benefit was confined to N0/1 patients with DFS being significantly longer in the neoadjuvant chemotherapy arm in this group

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Patients were treated with 3 courses ifosfamide (1.5 g m^2) and mesna (750 mg m^2) *bid*, plus cisplatin (25 mg m^2) and etoposide (100 mg m^2), all administered IV on days 1-3 every 3 weeks (ICE regimen) with G-CSF support; after 3 cycles, patients underwent radical surgery or were treated with two additional courses of ICE and/or curative RT	Phase II (b3/93; c2/97)➢ Italy ❑ 43 Stage IIIa (n=10) and IIIb (n=33) inoperable nsclc ❑ Regina Elena Cancer Institute (Rome, Italy) ❑ Scinto AF, etal, Br J Cancer, Nov 1999; 81(6): 1031-6	Grade 3-4 neutropenia occurred in 21% of 114 evaluable courses,but was of short duration, leading to neutropenic fever in 5% of the courses; severe thrombocytopenia and anemia were observed in 13% and 3% of the courses, respectively; nonhematologic toxicity was generally mild with only two episodes of reversible renal impairment	ORR was 69% (28 PR and 1 CR); 10 patients (8/10 patients in Stage IIIa and 2/33 patients in Stage IIIb) underwent radical surgery; median TTP for patients not undergoing surgery (n = 33) was 8 months (range=3-34+); median DFS for patients (n=10) rendered NED by surgery was 26 months (range=1-54+); median overall survival for the entire group was 12.5 months (range=2-57+)
A neoadjuvant (preoperative) regimen of cisplatin (100 mg/m^2), on day 1 and gemcitabine (1200 mg/m^2) on days 1 and 8, every 21 days, for a maximum of 6 cycles, was administered in an outpatient setting; 224 cycles were administered (mean=4.8). Salvage surgery was performed in 16 (34%) patients, involving 12 resections (26%) (Stage IIIa= 5, and Stage IIIb=7), and 4 exploratory thoracotomies	Phase II (b5/97; c5/99)➢ Spain ❑ 47 patients with unresectable N2-3 or T4 (Stage IIIA=18, and Stage IIIb=29; SCC=29, adenocarcinoma=14, and other=4) nsclc without malignant pleural effusion or vena cava syndrome ❑ Hospital de Cruces, Osakidetza (Bilbao, Spain) ❑ Rubio I, etal, ASCO00, Abs. 2122	Among 47 patients were evaluable for toxicity, there were 11 episodes of Grade III/IV neutropenia, 2 of thrombopenia, 18 of emesis, 25 of asthenia and 2 of arterial thrombosis; there were 2 toxic deaths	There were 4/47 (9%) CR, and 24/47 (51%) PR for an overall response rate of 60%; disease stabilized in 10 (21%), and progressed in 8 (17%). There were 9/47 (15%) patients alive free of disease, 6 after surgery at 4+, 5+, 5+, 9+, 16+, 29+ months, and 3 without surgery at +6, +8, and +15 months. MST was 9.8 months, 1-year survival was 61% and 2-year 31%, DFS at 1-year was 37% and at 2-years 6%
Combination Chemotherapy			
Two-Drug Regimens			
Patients were randomized to either IV cisplatin (100 mg/m^2), on day 1 of a 28-day cycle, or the combination of IV cisplatin (100 mg/m^2) on day 1, plus IV gemcitabine (1,000 mg/m^2) on days 1, 8, and 15 of a 28-day cycle	Phase II (b8/95; c2/97)➢USA ❑ advanced or metastatic nsclc ❑ Hoosier Oncology Group, the Walther Cancer Institute, Indiana University (Indianapolis, IN) ❑ Sandler AB, etal, J Clin Oncol, Jan 2000;18(1):122-30	Toxicity was predominantly hematologic and was more pronounced in the combination arm; Grade 4 neutropenia occurred in 35.3% of patients compared with 1.2% of patients on the cisplatin monotherapy arm and Grade 4 thrombocytopenia in 25.4% and 0.8%, respectively; neutropenic fever occurred in <5% in both arms and there were no serious hemorrhagic events related to thrombocytopenia in either arm	The combination of gemcitabine plus cisplatin demonstrated a significant improvement over single-agent cisplatin with regard to response rate (30.4% compared with 11.1%); median time to progressive disease was 5.6 months compared with 3.7 months and overall survival was 9.1 months compared with 7.6 months
Two different schedules of gemcitabine plus cisplatin were investigated, cisplatin (100 mg/m^2) was administered either on day 2, or day 15, with gemcitabine (1000 mg/m^2), standardized on days 1, 8 and 15	Phase II (multicenter randomized)➢Italy ❑ 88 newly diagnosed patients with Stage IIIb/IV nsclc ❑ Lucca Hospital (Italy) ❑ Ricci S, etal, ASCO99, Abs. 1853:480a	The toxicity profile was significantly lower in the day 15 arm, with Grade 3/4 thrombocytopenia occurring in 1.6% of patients versus 20% for the day 2 arm; anemia and neutropenia were negligible	Survival favored the day 15 cisplatin arm (without a statistically significant association)
Treatment with either IV gemcitabine (1,250 mg/m^2), on days 1 and 8, or IV etoposide (100 mg/m^2) days 1 to 3, along with IV cisplatin (100 mg/m^2), on day 1 was randomly administered in 21-day cycles	Phase III➢Spain ❑ 135 chemonaive patients with advanced nsclc ❑ Hospital Duran i Reynals (Barcelona, Spain) ❑ Cardenal F, etal, J Clin Oncol, Jan 1999;17(1):12-8	The overall toxicity profile for both combinations of drugs was similar; nausea and vomiting were more frequent in the gemcitabine arm but the difference was not significant; gemcitabine/cisplatin produced less Grade 3 alopecia (13% versus 51%) and Grade 4 neutropenia (28% versus 56%) but more	Response rate (externally validated) was superior in the gemcitabine/cisplatin arm (40.6% versus 21.9%) which was associated with a significant delay in time to disease progression (6.9 months versus 4.3 months) without impairment in QoL. There was no statistically significant difference

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		Grade 3 and 4 thrombocytopenia (56% versus 13%) than did etoposide/cisplatin but there were no thrombocytopenia-related complications in the gemcitabine arm	in survival time between both arms (8.7 months for gemcitabine-cisplatin versus 7.2 months for etoposide-cisplatin)
Patients were randomized to cisplatin (75 mg/m^2), and either paclitaxel, administered at 2 different dose levels (135 mg/m^{2}and 250 mg/m^2), or etoposide (100 mg/m^2), daily, on days 1 to 3; each regimen was repeated *q* 21 days; as a result this trial, paclitaxel (135 mg/m^2) combined with cisplatin has replaced etoposide plus cisplatin as the reference regimen in a recently completed phase III trial	Phase III➢USA ❑ 599 chemonaive Stage IIIb/IV nsclc ❑ Rush-Presbyterian St. Luke's Medical Center (Chicago, IL, USA); multicenter ❑ Bonomi P, etal, J Clin Oncol, Feb 2000; 18(3):623-31	With the exception of increased granulocytopenia on the low-dose paclitaxel regimen and increased myalgias, neurotoxicity, and, possibly, treatment-related cardiac events with high-dose paclitaxel, toxicity was similar across all 3 arms	In the combined paclitaxel regimens, MST was 9.9 months and 1-year survival rate was 38.9%; in the etoposide plus cisplatin arm, MST was 7.6 months and 1-year survival rate was 31.8%; there was no significant survival difference between the two paclitaxel dose levels; MST for the Stage IIIb subgroup was 7.9 months for etoposide group versus 13.1 months for the paclitaxel groups; MST for the Stage IV subgroup was 7.6 months in the etoposide group compared with 8.9 months in the paclitaxel groups; QoL declined significantly over the 6 months but scores were not significantly different among the regimens
Patients were treated with either cisplatin (80 mg/m^2) on day 1 and CPT-11 (60 mg/m^2) on days 1, 8 and 15 (regimen A=98 patients), or cisplatin (as above) and vindesine (3 mg/m^2) on days 1, 8 and 15 (regimen B=101 patients); both regimens were repeated every 4 weeks until disease progression	Phase III (b6/95, c10/97)➢ Japan ❑ 210 chemonaive patients with advanced (Stage IIIb=59% and IV=41%) nsclc ❑ National Cancer Center Hospital East (Kashiwa, Chiba, Japan) ❑ Niho S, etal, ASCO99, Abs. 1897:492a	Grade 3 toxicities were leukopenia 39%, 58%, neutropenia 63%, 83%, and diarrhea 13%, 1% on regimen A and B, respectively	After a median of 2 courses, among 98 evaluable patients on regimen A and 101 on regimen B, there were 28 (29%) and 22 (22%) objective responses, respectively; according to interim survival results on 203 eligible patients as of September 1998, MST was 45.4 and 49.6 weeks, for regimen A and B, respectively
Treatment consisted of 4-week courses of CPT-11 (60 mg/m^2) administered on days 1, 8, and 15, and a single dose of cisplatin (80 mg/m^2) after CPT-11 administration on day 1	Phase II➢USA ❑ 52 patients with inoperable Stage IIIb (n=11) and Stage IV (n=41) nsclc ❑ Vanderbilt University ❑ DeVore RF, etal, J Clin Oncol, Sep 1999;17(9):2710-20	Grade 3/4 adverse events consisted primarily of nausea (32. 7%) or vomiting (13.5%), late-onset diarrhea (17.3%), and neutropenia (46.1%); the study design led to preferential modification of CPT-11 doses, resulting in CPT-11 dose attenuations of ≥40 mg/m^2 in 31/52 (60%) patients whereas dose reductions of cisplatin were uncommon	ORR was 28.8% (15/52), MST was 9.9 months (range=1.6-30.8), and the 1-year survival rate was 37%
Gemcitabine (1000 mg/m^2) was administered IV weekly for 3 weeks, followed by 1 week rest and IV carboplatin (AUC=5) was administered immediately after gemcitabine on day 1 *q* 4 weeks	Phase II➢USA ❑ 7 patients with advanced nsclc ❑ Indiana University ❑ Ng EW, etal, Am J Clin Oncol, Dec 1999; 22(6):550-3	The protocol was prematurely terminated because of severe and unexpected hematologic toxicity; Grade 3-4 thrombocytopenia was observed in 4 of the first 5 patients during the first course of chemotherapy	There were no objective responses; MST=130 days
Patients were randomly assigned to either paclitaxel (200 mg/m^2), plus carboplatin (area under the curve = 6) on day 1 (group A), or paclitaxel in	Phase III➢Greece ❑ advanced and inoperable nsclc ❑ Hygeia Hospital (Athens, Greece) ❑ Kosmidis P, etal, Semin Oncol, Feb 2000; 27(1 Suppl 2):3-8	Preliminary results suggest that both combinations can be administered in full doses and are well tolerated; Grade 3/4 neutropenia was mild but more promi-	Among 127 eligible patients (63 in group A and 64 in group B) after a median follow-up time of 4.6 months, patients in group B experienced higher

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identical fashion to group A plus gemcitabine (1,000 mg/m^2) on days 1 and 8 every 3 weeks (group B); a minimum of 2 and a maximum of 6 cycles was allowed		nent in group A (10%) than group B (3%) while thrombocytopenia was not significant for either group; there was no severe neurotoxicity, hepatotoxicity, or cardiotoxicity in the vast majority of patients in either group	response rates (37.5%) than those in group A (21.8%), but the difference was not statistically significant
Treatment consisted of paclitaxel (200 mg/m^2), as a 1-hour IV infusion, and carboplatin (AUC=5) as a 30-minute IV infusion, *q* third week; a maximum number of 6 or 8 courseswere delivered to late responders; betamethasone was administered 40 minutes prior to infusion and clemastin and cimetidine 10 minutes later	Phase II➢Sweden ❑ 60 patients with Stage IIIb (n=45%) and Stage IV (n=55%) nsclc ❑ Orebro Medical Centre Hospital (Sweden) ❑ Helsing M, etal, Lung Cancer, May 1999; 24(2):107-13	Hematologic toxicity was mild with no Grade 4 leukopenia; only 7 patients (11%) experienced Grade 3 leukopenia; there was no Grade 4 toxicity; Grade 3 toxicity included myalgia (5%), allergic reaction (3%) and peripheral neuropathy (6%); dose was reduced in 15% of patients because of neurotoxicity; hematologic toxicity was much milder than expected, probably because of more exact determination of the glomerular filtration rate (GFR)	There was 1 CR and 18 PR for an ORR of 29%; 28% of patients stabilized and 40% progressed during treatment; median TTP was 22 weeks and the 1-year survival rate was 38%; MST was 41 weeks
Paclitaxel (200 mg/m^2) was administered as a 3-hour infusion, followed by carboplatin (AUC=6), repeated *q* 3 weeks for six courses; subcutaneous G-CSF (5 mgram/kg) was injected during subsequent courses if there was Grade 3-4 leukopenia or granulocytopenia in the previous course	Phase II (b4/96; c7/97)➢ Thailand ❑ 53 chemonaive patients (adenocarcinoma=64%) with Stage IIIb and Stage IV (62%) nsclc ❑ Rajavithi Hospital (Bangkok, Thailand) ❑ Laohavinij S, etal, Lung Cancer, Dec 1999;26(3):175-85	Among 56 patients evaluable for toxicity, Grade 3 and 4 granulocytopenia, anemia and thrombocytopenia were observed in 25%, 3%, and 1%, respectively; G-CSF was required in 28% of 272 courses administered; there were 4 (1.5%) episodes of febrile neutropenia, 3 (1%) of angina pectoris and 1 (0.4%) of anaphylaxis; other common toxicities, including myalgia, arthralgia, peripheral neuropathy and asthenia were generally mild; most toxicities showed a cumulative effect	36 (68%) patients completed all six cycles; ORR was 55% (CR=4%, CR=51%, SD=30%; PD=15%); median PFS time for all patients was 28 weeks (range=18-37), 31 weeks (range=21-41) for Stage IIIb and 22 weeks (range 16-29) for Stage IV; MST was 55 weeks (range=51-59), and 1-year survival rate was 55%; MST and 1-year survival rate was higher for Stage IIIb patients (75 weeks versus 46 weeks)
Docetaxel (100 mg/m^2) was administered once every 6 weeks from week 1 and cisplatin (120 mg/m^2 for two doses and 100 mg/m^2 thereafter), once *q* 6 weeks from week 4, for 6 cycles (3 docetaxel and 3 cisplatin); a median of 5 cycles was administered, with no dose reductions	Phase II➢Finland ❑ 44 patients with advanced nsclc ❑ Helsinki University Central Hospital (Finland) ❑ Mattson K, etal, Anticancer Drugs, Jan 2000; 11(1):7-13	Most frequent Grade 3-4 toxicities were nausea (23% of patients), vomiting (18%) and neutropenia (77%); infections were also common, but not severe	Among 36/44 patients evaluable for efficacy, PR rate was 36% (13/36 patients), and disease stabilized in 42%(15/36); median duration of response was 10.5 months and MTP was 4.5 months; MST was 9 months; the 1- and 2- year survival rates were 39 and 16%, respectively
Vinorelbine (20 mg/m^2) followed by gemcitabine (800 mg/m^2), on days 1, 8, and 15, *q* 4 weeks	Phase II (c99)➢Taiwan ❑ 40 patients with advanced (Stage IIIb/IV) nsclc ❑ Veterans General Hospital (Tapei, Taiwan); multicenter ❑ Chen YM, etal, ASCO99, Abs. 1856:481a	Grade 3 and 4 hematologic toxicity was significant for neutropenia (47.5%), leukopenia (52.5%) and thrombocytopenia (20%)	Among 40 patients assessable for toxicity and response, there was 1 (2.5%) CR and 27 (67.5%) PR, for an ORR of 67.7%; MST was 12 months

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Treatment involved IV vinorelbine (20 mg/m^2), followed by IV gemcitabine (1000 mg/m^2), on days 1, 8, and 15, repeated *q* 28 days	Phase II (b1/98, c9/98)➢USA ❑ 36 patients with nsclc whose disease had progressed after treatment with a taxane (n=1), a platinum agent (n=4), or both (n=31) (second-line treatment) ❑ Minnie Pearl Cancer Research Network ❑ Gian V, ASCO99, Abs. 1949:505a	Grade 3/4 toxicity included leukopenia (25%), anemia (22%), thrombocytopenia (19%), fever (19%),and fatigue (16%); there was one (3%) septic death	Among evaluable patients, there were 7 (21%) objective responses (PR=6 and CR=1), and 15 (45%) minor response/ SD; 13 patients remained progression-free after a median follow-up of 4 months
Vinorelbine (45 mg/m^2) was administered by IV push, followed by docetaxel (60 mg/m^2) infused over one hour, administered *q* 2 weeks with subcutaneous G-CSF (5 mg/kg), on days 3-12; supportive therapies included oral dexamethasone (8 mg), *bid*, for 5 doses, starting 24 hours before docetaxel infusion, and oral ciprofloxacin (500 mg), *bid*, on days 3-9; the median number of cycles administered was 10 (2-27)	Phase II➢USA ❑ 35 chemotherapy-naive patients with advanced nsclc (Stage IV=91%) nsclc ❑ Memorial Sloan-Kettering Cancer Center ❑ Krug LM, etal, ASCO99, Abs. 1775:460a	There was no Grade 3/4 neuropathy, thrombocytopenia, or vomiting, other toxicities included neutropenic fever (23%), dyspnea/infiltrates (34%), onycholysis (43%), and lacrimation (77%); because of cumulative adverse effects, application of this regimen for a shorter period, such as in a neoadjuvant setting, may provide optimal benefit while minimizing toxicity	Among evaluable patients, 19/35 (54%) experienced PR; median duration of response was 6+ months (range=4 to 16+ months); predicted 1-year survival after a median follow-up of 7 months was 86%
Patients were treated with weekly vinorelbine (20 mg/m^2) with dexamethasone premedication, and escalated doses of docetaxel; MTD without G-CSF for docetaxel was 25 mg/m^2 per week; with G-CSF, in chemonaive patients, it was 35 mg/m^2 per week; patients were assessed for response at 9 and 18 weeks	Phase I (b5/97, c8/98)➢USA ❑ 21 patients (Stage IIIb=2, IV=13, recurrent=6) nsclc ❑ Duke University Medical Center and Veterans Affairs Hospital, Durham ❑ Johnston E, etal, ASCO99, Abs. 1838:476a	One patient died with neutropenic sepsis, and 1 from pulmonary complications of multifactorial etiology	PR was 28% and the ORR was 40% in previously untreated patients
Patients were treated with vinorelbine (25 mg/m^2), administered as a 10-minute IV infusion, followed by gemcitabine (1200 mg/m^2), as a 30-minute infusion, on days 1, 8 and 15; antiemetics were used but no prophylactic hematopoetic growth factors; treatment cycles were repeated *q* 4 weeks up to a total of 8 cycles unless there was an indication of progressive disease	Phase II➢Austria ❑ 70 chemotherapy-naive patients with advanced (Stage IIIb=19%, Stage IV=81%) nsclc ❑ University of Vienna (Austria) ❑ Pirker R, etal, ASCO99, Abs. 1849:479a	Among 33 patients evaluable for toxicity, Grade 3/4 neutropenia occurred in 55% anemia in 12% and thrombocytopenia in 15%; nonhematologic toxicities that included nausea, flu-like symptoms, thrombophlebitis and elevation of liver enzymes, were mild	Among 60 evaluable patients, PR rate was 19%, stable disease rate 34%, and progressive disease rate 33%; MST was 9 months
Patients were treated with gemcitabine (1250 mg/m^2) over 30 minutes (1000 mg/m^2 for the first 6 patients) and vinorelbine (25 mg/m^2) over 6 minutes, both administered IV on days 1 and 8, *q* 21 days; treatment was planned for a total of 6 cycles or more if there was persistent benefit; growth factors were not allowed	Phase II➢USA ❑ 33 chemonaive patients with Stage IIIb (malignant pleural effusion), or Stage IV nsclc ❑ Mount Sinai Comprehensive Cancer Center (Miami Beach, FL); multicenter ❑ Lilenbaum R, etal, Cancer, 1 February 2000;88(3):557-62	Grade 3 and 4 neutropenia was observed in 13% and 25% of the 148 treatment cycles, respectively; one patient died of neutropenic sepsis; there were only 2 episodes of Grade 3 and 4 thrombocytopenia and nonhematologic toxicity was minimal	Among all 32 eligible patients, the ORR was 25%, PR was 25% (8/32); MST was 8.3 months, and the 1-year survival rate was 38%; MST of patients with PS 0-1 was 11.7 months and the 1-year survival rate was 48%

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Vinorelbine (20 mg/m^2) followedby gemcitabine (1000 mg/m^2) was administered to all patients on days 1, 8, and 15 of each 28-day cycle; patients were re-evaluated for response after two treatment courses and responding patients, and those with stable disease, were treated with a maximum of six courses	Phase II (b1/98; c11/98)➢ USA ❑ 55 patients [47 (85% had been previously treated with both a taxane and a platinum agent] with advanced nsclc ❑ Sarah Cannon Cancer Center ❑ Hainsworth JD, etal, Cancer, 15 Mar 2000;88(6): 1353-8	The regimen was well tolerated with few nonhematologic toxicities and no alopecia; Grade 3 neutropenia and thrombocytopenia occurred in 27% and 22% of patients, respectively, but Grade 4 neutropenia was uncommon, occurring in 9% of patients; only 4 patients required hospitalization for treatment-related neutropenia and fever	Among 50 evaluable patients ORR was 18% (9/50); PR was 16% (8/50) and CR was 2% (1/50); MST was 6.5 months with an actuarial 1-year survival of 20%; minor response or stable disease were observed in 48% (24/50); MTP for patients with objective response or SD was 5 months
Vinorelbine (35 mg/m^2) and gemcitabine (1200 mg/m^2) wereeach adminisrtered on days 1 and 15 of a 28-day cycle; treatment consisted of 3 cycles of chemotherapy, with a further 3 cycles administered to those who responded (SD or CR/PR) to the first 3 cycles; patients who achieved CR or PR after 6 cycles continued with the treatment until relapse	Phase II➢Finland ❑ 33 patients with Stage IIIb/IV inoperable nsclc ❑ Helsinki University Central Hospital ❑ Isokangas OP, etal, Ann Oncol, Sep 1999; 10(9):1059-63	Grade 3/4 neutropenia occurred in 8/33 (24%) patients, resulting in dose reductions or delays for 3 (9%); no thrombocytopenia or anemia occurred	Among 28 patients evaluable for response, ORR was 46% (13/28), CR rate was 11% (3/28), PR rate was 36% (10/28) and disease stabilized in 25% (7/28); the 1-year cumulative survival rate was 24%; median time-to-progression was 4 months (range=1-16 months) and MST was 8 months
Vinorelbine (30 mg/m^2) was administered IV on day 1 and 8, and IV cisplatin (100 mg/m^2) on day 1 with the cycle repeated *q* 3 weeks; a total of 153 courses were administered with patients treated with a median dose intensity of 81.7% for vinorelbine and 74.1% for , cisplatin	Phase II (b9/95; c12/96)➢ Republic of South Africa ❑ 35 patients with locally advanced or disseminated nsclc ❑ National Hospital (Bloemfontein, Republic of South Africa) ❑ Goedhals L, etal, Curr Med Res Opin 1999;15(3):185-92	Toxicity was manageable, consisting of Grade 3 nausea and vomiting (45% of patients), Grade 3/4 neutropenia occurring in 13 patients with 3 patients experiencing Grade 3 infection; Grade 3 constipation occurred in 9.1% of patients; other side effects were mild	14/35 (40%) patients achieved a response, including 1/35 (2.9%) CR and 13/35(37.1%) PR; median time to progression was 6.4 months (range=12-572 days); MST was 15.7 months (range=12-882+ days); 1-year survival was 56%
Treatment consisted of IV vinorelbine (30 mg/m^2), administered on days 1 and 5, of a 21-day cycle, and cisplatin (100 mg/m^2, reduced to 80 mg/m^2 after the first seven patients) administered on day 1; a total of 211 courses were administered with the median number of cycles administered per patient being 4.5 (range=1-6), the median dose intensity for vinorelbine was 16.9 mg/m^2/ week (84.4%), whereas that of cisplatin was 22.8 mg/m^2/week (84.7%)	Phase II (b4/96; c5/97)➢ Taiwan ❑ 52 patients with Stage IIIb or IV nsclc ❑ Veterans General Hospital-Taipei (Taipei, Taiwan) ❑ Perng RP, etal, Am J Clin Oncol, Feb 2000;23(1):60-4	Among 50 patients evaluable for both response and toxicity, Grade 3 or 4 nausea/vomiting occurred in 58% of patients, anemia in 41%, neutropenia in 12%, and diarrhea in 14%	25/50 patients responded to the therapy; ORR was 50%, and the CR rate was 2%; median duration of responses was 9 months and median time to disease progression was 6.8 months (range=0.4-18.1 months); MST was 13 months and 54% of patients were alive at 1 year
This regimen was based on results from a phase I clinical trial that enrolled 18 patients to determine MDT; in the phase II trial, epirubicin (100 mg/m^2) was administered on day 1 and gemcitabine (1125 mg/m^2) on days 1 and 8 of a 21-day cycle	Phase I and II➢The Netherlands ❑ 43 chemotherapy-naive patients with Stage IIIb and Stage IV (n=74%) nsclc ❑ University Hospital (Groningen, The Netherlands) ❑ Van Putten JW, etal, Br J Cancer, February 2000;82(4): 806-11 and Van Putten JWG, etal, ASCO99 Abs. 1879:487a)	Hematologic toxicity was significant with Grade 3 and 4 neutropenia seen in 66% of patients, leukopenia in 58.5%, thrombocytopenia in 25.6%, and anemia in 12%; Grade 4 granulocytopenia occurred in 32.5% and Grade 4 thrombocytopenia in 11.6% of cycles; febrile neutropenia occurred in 6 patients; nonhematologic toxicity was mainly Grade 2 and 3 mucositis in 35% of patients	Response rate was 49%, consisting of 3 CR and 18 PR, MST was 42 weeks and the 1-year survival was 49%

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CPT-11 (60 mg/m^2) and cisplatin (80 mg/m^2) were administered by IV drip infusion, on days 1, 8, 15 and only on day 1, respectively, repeated *q* 4 weeks	Phase II (b2/92; c9/92)➢Japan ❑ 102 advanced-stage nsclc patients; group A included 70 chemonaive patients (Stage III=26 and Stage IV=43 with SCC=15, adenocarcinoma=51 and large-cell lung cancer=3) and group B 32 pretreated patients (Stage I=1, Stage IIIb=7 and Stage IV=24 with SCC=2, adenocarcinoma=28 and other =2) ❑ Chiba University (Chiba, Japan) ❑ Nagao K, etal, Gan To Kagaku Ryoho March 2000; 27(3):413-21	Major adverse reactions (Grade 3 or higher) in Group A/Group B were neutropenia (80.3%/73.3%), anemia (35.3%/34.4%), diarrhea (18.8%/28.1%) and nausea/vomiting (34.8%/34.4%)	Among 69 evaluable patients in Group A the ORR was 47.8% (33/69) and MST was 308 days; among 32 evaluable patients in Group B, the ORR was 25.0% (8/32) and MST was 295 days
Treatment consisted of CPT-11 (80 mg/m^2) administered IV over 90 minutes, on days 1, 8, 15, and ifosfamide (1500 mg/m^2) administered IV (with Mesna), over 90 minutes, on days 1to 3, of a 28-day cycle; 113 cycles were administered	Phase II (b2/97, c5/99)➢Japan ❑ 41 chemotherapy-naive patients with advanced (Stage IIIb=8 and Stage IV=33; adenocarcinoma=28, SCC=10, large-cell=3) nsclc ❑ Kurume University, School of Medicine (Kurume, Japan) ❑ Masao I, etal, ASCO00, Abs. 2061	Grade 3 or 4 toxicity consisted of neutropenia (39%), leukopenia (24%), and diarrhea (7%); other Grade 3/4 toxicities were rare, including thrombocytopenia, anemia, pnumonitis, cystitis, and nausea and vomiting	ORR was 29.3%, consisting of 12 PR
UFT (400 mg/m^2) was administered orally on days 1-14, and cisplatin (80 mg/m^2) was injected IV on day 8; treatment was repeated every 3-4 weeks	Phase II➢Japan ❑ 108 previously untreated Stage IIIb and Stage IV (70%) nsclc ❑ National Kyushu Cancer Center ❑ Ichinose Y, etal, Cancer, 15 Jan 2000;88(2):318-23	All 108 patients were assessable for toxicity and survival; Grade 3 leukopenia and thrombocytopenia were observed in only 1 (0.9%) and 3 patients (2.8%), respectively; Grade 3/4 non-hematologic toxicities included elevated bilirubin (6.5%) and emesis (7.4%); one patient with a past history of duodenal ulcer died of ulcer perforation 15 days after completing the first treatment cycle	Among 103 patients evaluable for response, the ORR was 29.1% (CR=1%, PR=28.1%); MST was 40 weeks; the 1-year survival rate was 39%; median PFS time was 28 weeks
Three-Drug Regimens			
Patients were treated with cisplatin (40 mg/m^2) on days 1, 2, 3, ifosfamide (1800 mg/m^2) days 22, 23, 24, and vinorelbine on (30 mg/m^2) on days 1, 8, 22, 29, *q* 6 weeks up to 6 courses	Phase II➢Italy ❑ 70 chemoradiotherapy-naive patients with Stage IIIa, Stage IIIb, or Stage IV nsclc ❑ Universita Cattolica del Sacro Cuore (Rome, Italy) ❑ Barone C, etal, Oncology 2000;58(1):25-30	Toxicity was mainly hematologic, but was not dose-limiting and was easily manageable	Among 67 evaluable patients, the ORR was 47.8 ± 12% with responses occurring more frequently in patients with locally advanced (Stage IIIa/IIIb) disease and/or PS 0; MST was 12 months (19.9 months in Stage III patients who had an integrated treatment and 10 months of metastatic disease); median time to treatment failure was 10.5 months
Patients were treated with cisplatin (20 mg/m^2) on days 1-3, ifosfamide (1500 mg/m^2), on days 1-2 (plus mesna as uroprotector), and vinorelbine (25 mg/m^2), on days 1 and 5; filgrastim (300 mgm) was administered subcutaneously from days 8 to 15	Phase II➢Italy ❑ 29 patients with advanced nsclc ❑ Ospedale S. Andrea (La Spezia, Italy) ❑ Tognoni A, etal, J Chemother, Aug 1999; 11(4):306-9	Toxicity was acceptable	Overall response rate was 28%

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This clinical trial compared a 3-drug combination involving a regimen that had been tested in previous phase I (Frasci G, etal, Ann Oncol 1997) and phase II trials with 2 two-drug regimens; patients were randomized to arm A, consisting of cisplatin (50 mg/m^2), gemcitabine (1,000 mg/m^2), and vinorelbine (25 mg/m^2), on days 1 and 8, every 3 weeks (PGV regimen); arm B, consisting of cisplatin (100 mg/m^2) on day 1, and gemcitabine (1,000 mg/m^2) on days 1, 8, and 15, *q* 4 weeks (PG regimen); or arm C consisting of cisplatin (120 mg/m^2) on days 1 and 29, and weekly vinorelbine (30 mg/m^2) weekly (PV regimen); because of favorable MST with the PVG regimen, accrual in the PV was stopped but enrollment continued in the PGV and PG arm	Phase III (b4/97; c12/99)➢ Italy ❑ chemonaive patients with advanced (Stage IIIB and IV) nsclc ❑ Southern Italy Cooperative Oncology Group (SICOG) of the National Tumor Institute (Naples, Italy) ❑ Comella P, etal, J Clin Oncol, Apr 2000;18(7):1451-7 and ASCO99, Abs. 1876:486a	An interim analysis involving 180 patients (Stage IIIb=63 and Stage IV=117) randomized between March 1997 and October 1998, showed no unexpected toxicity in the 3 arms; neither hematologic nor nonhematologic toxicities were substantially worse in those treated with the PGV regimen	Of 180 patients (Stage IIIb=76 and Stage IV=104), 128 patients (PGV=33, PG=42, PV=53) died from their disease; MST was 51, 42, and 35 weeks in PGV, PG, and PV regimens, respectively; the corresponding 1-year projected survival rates were 45% for PGV, 40% for PG, and 34% for PV; ORR was 47% for PGV, 30% for PG, and 25% for PV; there was an even more significant difference in MST when only Stage IV disease was considered which was 47 weeks with PVG compared to 34 weeks with PG and 27 weeks with PV. At a 13-month median follow-up, MST for the entire population, was 45 weeks; PGV regimen was associated with a substantial survival gain (MST > 3 months longer) when compared with the PV combination
Treatment consisted of paclitaxel (110 mg/m^2) and cisplatin (60 mg/m^2), on day 1 and 15, with gemcitabine (800 mg/m^2) on day 1, 8, and 15, administered every 4 weeks; 6 patients (Group 1) were treated with chemotherapy as described above, while 43 (Group 2) were not administered gemcitabine on day 8	Phase II➢Denmark ❑ 49 previously untreated patients with advanced nsclc ❑ National University Hospital/ Rigshospitalet (Copenhagen, Denmark) ❑ Sorensen JB, etal, Ann Oncol, September 1999; 10(9):1043-9	All patients in Group 1 experienced Grade 4 neutropenia, and 4 achieved a PR (67%); in Group 2, Grade 4 neutropenia occurred in 58%, with one episode of febrile neutropenia; no other Grade 4 toxicities occurred, while Grade 3 thrombocytopenia occurred in 9%, nausea/vomiting in 12%, neurotoxicity in 12%, and nephrotoxicity in 7%; neutropenia is the DLT of this combination regimen, but septicemic episodes were rare and there were no toxic deaths	There were 3 CR and 20 PR, for an overall response rate of 54%; median response duration was 29 weeks (range=10-66+), median time to progression was 28 weeks (range=4-66+), and MST was 46 weeks (range=4-89+); 1-year survival rate was 42%
Treatment consisted of paclitaxel (80 mg/m^2), and gemcitabine (1000 mg/m^2), both administered on days 1 and 8, and cisplatin (70 mg/m^2), administered on day 1, of a 21-day cycle; a total of 82 courses were administered (median=2.6)	Phase II➢Spain ❑ 31 patients with inoperable (Stage IIIb=12 and Stage IV=12) nsclc ❑ Hospital Arnaud de Vilanova (Lerida, Spain) ❑ Morales S, etal, ASCO00, Abs. 2167B	Among 29 evaluable patients, Grade 3/4 granulocytopenia occurred in 3%, anemia in 4%, and thrombocytopenia in 2%; the most common non-hematologic toxicity was asthenia which included Grade 2 in 26 cycles (31%), Grade 3 in 3 cycles (3%), and Grade 4 in 1 (1%)	ORR was 55% (16/29), with a CR of 7% (2/29), and a PR of 48% (14/29)
Patients were treated with IV paclitaxel (200 mg/m^2), delivered over 1 hour on day 1, IV carboplatin (AUC=6.0), also on day 1, and IV vinorelbine (22.5 mg/m^2), on days 1 and either 8 or 15; the regimen was repeated *q* 21 days; patients were reassessed after two courses, and responders continued treatment for a maximum	Phase II (b6/91; c8/98)➢USA ❑ 89 treatment-naive patients with advanced (Stage IIIb=32 and Stage IV=58) nsclc ❑ Minnie Pearl Cancer Research Network ❑ Grimaldi M, ASCO99, Abs. 1954:507a, and Hainsworth JD, Chemotherapy Foundation Symposium XVI, 11-13 November 1998, Abs. 76:92-93	Myelosuppression was the major toxicity with Grade 3/4 leukopenia and thrombocytopenia occurring in 73% and 3% of patients, respectively; there were 37 episodes of febrile neutropenia among 32 patients, and 4 (4%) treatment-related deaths attributable to infection; there were 2 (2%) additional sudden deaths at home that	ORR was 35% (31/89 patients); PR was 29% and CR 2%; MST was 9 months; actuarial 1-year survival was 48%

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of 8 courses; this regimen with the vinorelbine dose reduced to 20 mg/m^2 is being evaluated as a one arm of an ongoing four-arm randomized phase III trial in patients with advanced nsclc		may have been treatment-related; Grade 3/4 nonhematologic toxicities included fatigue (24%), neuropathy (12%) and nausea and vomiting (10%); addition of vinorelbine substantially increased toxicity	
Treatment consisted of gemcitabine (1000 mg/m^2), on days 1 and 8, ifosfamide (3 g/m^2), on day 1, and cisplatin (50 mg/m^2), on day 1, administered in 21-day cycles; a maximum of 6 cycles were administered	Phase II (b3/96; c12/97)➢ Spain ❑ 60 chemonaïve patients with Stage III (n=37), and Stage IV (n=23) nsclc ❑ Hospital del Mar (Barcelona, Spain) ❑ Vandell-Nadal C, etal, Lung Cancer, 1 May 2000: 28(2): 109-115	The most frequent toxicity was hematologic; Grade 3 or 4 myelotoxicity occurred in 56% of patients in one of the cycles, although only 7 episodes of febrile neutropenia were recorded in the 255 cycles administered	Among 59 patients evaluable for response, the ORR was 43%, with 3% CR, 40% PR and 22% SD; MST was 52 weeks for the whole group (65 and 35 for patients with Stage III and Stage IV disease, respectively)
Patients were treated with a MEP regimen consisting of IV cisplatin (80 mg/m^2), on day 1, and IV etoposide (80 mg/m^2), on days 1, 2, and 3, *q* 3 weeks along with IV mitomycin C (10 mg/m^2) on day 1, of the first and third cycles for a median of 4 cycles (range=1-11); palliative RT was administered to 10 patients (15%) before MEP and to 17 (25%) concurrent with MEP	Phase II➢USA ❑ 68 patients (9 had relapsed after being treated for early-stage nsclc) with Stage IIIb (pleural effusion) or IV [80% with stable disease, and 14 (21%) with brain metastases at diagnosis] nsclc ❑ Wayne State University (Detroit, MI) ❑ Ali MA, Kraut MJ, etal, Cancer Invest 2000;18(1):1-5	The major toxicity of MEP was myelosuppression, with Grade 3-4 neutropenia seen in 74% of patients; 16 patients (24%) had documented infections, and there were 8 (12%) treatment-related deaths	PR rate was 35% with a median duration of 4.4 months, (range=1.4-13 months); MST was 8.1 months (range=1-34 months), and 1-year survival was 32%
Cisplatin (15 mg/m^2), carboplatin (200 mg/m^2), and vindesine (3 mg/m^2) were administered on day 1, and cisplatin was administered on days 2-5, and vindesine was administered on day 8	Phase II➢Japan ❑ 24 chemonaïve patients with advanced, inoperable nsclc ❑ Sapporo City General Hospital (Japan) ❑ Haneda H, Gan To Kagaku Ryoho, February 2000;27(2):227-31	Major toxicities were hematologic; Grades 3 and 4 leukopenia occurred in 25% patients, and thrombocytopenia in 21%	The overall MST was 72 weeks, and the 1-year survival rate was 57%
Patients were treated on an outpatient basis with IV carboplatin (AUC=5) and IV gemcitabine (800 mg/m^2), on day 1, and IV docetaxel (75 mg/m^2) and IV gemcitabine (800 mg/m^2) on day 8; subcutaneous G-CSF (150 mg/m^2) was administered prophylactically on days 3-6 and 10-16; chemotherapy was repeated *q* 4 weeks and patients were evaluated for response *q* 2 cycles. All 45 patients were assessable for toxicity, and 41 were assessable for response	Phase II➢Greece ❑ 45 chemotherapy-naive patients (SCC= 51.2% and poorly differentiated SCC=37.8%) with Stage IIIb (n=9) and Stage IV (n=36) nsclc ❑ Metaxas Memorial Cancer Hospital (Piraeus, Greece) ❑ Pectasides D, etal, J Clin Oncol, Dec 1999;17(12): 3816-21	Grade 3/4 anemia and thrombocytopenia occurred in 17.7% and 28.8% of patients, respectively; 21 patients (46.6%) developed Grade 3/4 neutropenia, with 6 patients (13.3%) having fever; alopecia was universal; Grade 3 diarrhea occurred in 4 patients (8.8%), Grade 3/4 neurotoxicity in 10 (22.2%), and Grade 2/3 allergic reaction in 3 (16.6%); there were no treatment-related deaths; 6 patients (13.3%) required a dose reduction, 2 of whom required two reductions	On an intent-to-treat analysis, the objective response rate was 46 5% (21/45 patients); among the 45 patients, CR was 8.8%, PR was 37.7%, and disease stabilized in 15.5% and progressed in 31.1%; MST was 13.5 months; the actuarial 1-year survival rate was 51.11%; the median duration of response was 7.6 months, and the time to tumor progression was 8.1 months
Patients were treated with fixed doses of 3 drugs, IV paclitaxel (175 mg/m^2) over 3 hours, IV carboplatin (AUC=5) over 0.5 hours, and IV CPT-11 (100 mg/m^2) over 1.5 hours on day 1, every 3 weeks	Phase II➢USA ❑ 40 patients with Stage IIIb or IV nscl ❑ Cedars-Sinai Medical Center (Los Angeles, CA) ❑ Langdon L, etal, ASCO99, Abs. 1834:475a	Grade 3/4 neutropenia was 71% with Grade 3/4 vomiting seen in 15%	Among 33/40 patients, the objective response rate was 60.6% (45.5% confirmed response rate) with a CR rate of 3% and PR rate of 42.4%; 1-year survival was 46.9%

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Patients were randomized to either gemcitabine (1,000 mg/m^2), on days 1, 8, and 15, plus cisplatin (100 mg/m^2), on day 2, *q* 28 days, or mitomycin (6 mg/m^2), plus ifosfamide (3,000 mg/m^2), and mesna, on day 1 plus cisplatin (100 mg/m^2) on day 2, every 28 days	Phase III➢Italy ❑ 307 patients with Stage IIIb (limited to T4 for pleural effusion and N3 for supraclavicular lymph nodes) or Stage IV nsclc ❑ Policlinico Hospital (Perugia, Italy) ❑ Crino L, etal, J Clin Oncol, Nov 1999; 17(11):3522-30	Grade 3 and 4 thrombocytopenia at 64% was significantly worse in the gemcitabine/cisplatin arm compared to 28% in the mitomycin/ifosfamide/cisplatin arm, whereas Grade 3 and 4 alopecia was more common in the mitomycin/ifosfamide/cisplatin arm (39% versus 12%)	No major differences in changes in QoL were observed between the two treatment arms; the objective response rate was 38% in the gemcitabine/cisplatin arm compared with 26% in the mitomycin/ifosfamide/cisplatin arm and MST was 8.6 months and 9.6 months, respectively
Treatment consisted of tamoxifen (150 mg/m^2), daily, divided into 4 doses, for 8 days, and cisplatin (60 mg/m^2), on day 4, and etoposide (60 mg/m^2) daily on days 4 to 8; patients remained in the study either until intolerable toxicity or disease progression occurred; 191 cycles were delivered	Phase II➢Taiwan ❑ 40 patients with inoperable Stage IIIb/IV nsclc, or recurrent disease ❑ National Taiwan University Hospital (Taipei, Taiwan) ❑ Yang CH, etal, Cancer, 1 Aug 1999; 86(3):415-20	Increased thrombotic episodes were noted; all were clinically manageable	All patients were evaluable for response and toxicity; there was 1 CR and 14 PR for an ORR of 37.5%; MST was 47 weeks; 1-year survival was 44%
Four-drug Dose-intensive Chemotherapy			
A modified protocol from that used in phase I, consisted of ifosfamide (2,000 mg/m^2) on days 1-3 (with mesna), paclitaxel (225 mg/m^2) by a 3-hour infusion on day 1, carboplatin (AUC=5) on day 2, and etoposide (75 mg/m^2) on days 1-3; G-CSF (5 mg/kg/day) was administered from day 4 until the neutrophil count was 3,000 mm^3	Phase I➢USA ❑ Stage IIIb and IV nsclc ❑ Massachusetts General Hospital, and Brigham & Women's Hospital (Boston, MA) ❑ Strauss GM, etal, ASCO99, Abs. 1855:481a	There were no treatment-related deaths, and relatively few patients experienced severe toxicity with Grade 4 neutropenia only observed in 5%. and Grade 3 gastrointestinal, neuromuscular, or hematologic toxicity in 34%	At a median follow-up of 12 months, among 36 evaluable patients, the ORR was 17%; CR rate was 3%, PR rate was 14%, and disease stabilized in 61%, and progressed in 22%; among 27 evaluable patients with adenocarcinoma, RR was 15% (4% CR, 11% PR, 67% SD, 18% PD), while among 9 with other histologies, it was 22% (22% PR, 45% SD, 33% PD); MST of all 41 patients was 11.3 months, and 1- and 2-year survival was 39% and 0%, respectively

Legend: ***CR****=complete response* ***DLT****=dose-limiting toxicity* ***MDT****=maximum tolerated dose* ***MST****=median survival time* ***MTP****=median time to progression* ***NE****=nonevaluable* ***ORR****=overall response rate* ***PFS****=progression-free survival* ***PR****=partial response* ***PS****=performance status* ***QoL****=quality of life* ***SD****=stable disease* ***TTP****=time to progression*

*Source: NEW MEDICINE Oncology KnowledgeBASE (∩∩|**OK**), June 2000*

OTHER TREATMENT APPROACHES

Other treatment approaches, such as various local interventions, are used for palliation to improve patients' QoL and, rarely, with curative intent. Approximately 30% of nsclc patients present with obstruction of the trachea and main bronchi which lead to respiratory distress, bleeding and infection. Similar problems are caused by pulmonary metastases arising form other types of primary tumors. Early reopening and treatment of blocked airways is required to improve symptoms and QoL. Interventions, such as brachytherapy, neodymium:yttrium-aluminum garnet (Nd-YAG) laser ablation, cryotherapy, electrocautery, photodynamic therapy (PDT), and prosthetic stents, are used to maintain an open lumen in patients with early-stage lung cancer, or to reopen an obstructed bronchial lumen in patients with inoperable obstructive bronchial tumors. None of these interventions, however, is considered to be a "gold standard".

Laser Ablation

Laser treatment is mainly used to obtain bronchial patency rapidly, but needs to be followed up with other treatments. Nd-YAG laser endoscopic treatment for malignant endobronchial obstruction is an established technique, indicated for tumors that are relatively short in length, and are situated in the trachea, mainstem or proximal lobe bronchi. Selected patients with intrinsic endobronchial obstructing lesions, or extrinsic compression attributed to tumor, were successful palliated with endobronchial laser therapy (Miller JI and Phillips TW, Annals of Thoracic Surgery 50(2):190-196, 1990).

Photodynamic Therapy (PDT)

PDT based on Photofrin (Exhibit 5) as the photosensitizer, is an approved treatment approach in nsclc (for more information on PDT applications in cancer, in general, see FO, pp 29, 56, 64, 101-102, 239, 271-272, 296 and 369,

494-495, 589, and 918-923). PDT for the treatment of lung cancer has been carried out in Japan, since 1978, and has been approved in the USA since 1998. PDT has been applied clinically to both early and advanced stages of lung cancer, and in combination with surgery. It can preserve pulmonary function, is well tolerated, and is cost-effective in comparison with other treatments. PDT is an effective modality, particularly in the treatment of bronchogenic SCC. PDT can also be curative in cases of early-stage central type SCC, and may be an alternative to surgery in patients with *in situ* carcinoma, or minimally invasive SCC. PDT is also useful in treating patients with non-primary lung cancer metastatic to the bronchi (McCaughan JS Jr, Lasers Surg Med 1999;24(3):194-201). When PDT was performed in 26 early bronchogenic cancers in 23 patients at Ospedale Bellaria-Maggiore (Bologna, Italy), there were 16 CR and 10 PR (Patelli M, etal, Monaldi Arch Chest Dis, Aug 1999;54(4):315-8).

The vast majority of PDT applications use light waves in the 350-800 nanometer range from the visible portion of the light spectrum which penetrate up to 3 cm deep into human tissue. Most PDT in nsclc is performed using 630-nm light, usually generated by an argon dye laser, delivered through cylinder diffusing tip quartz fibers passed through the biopsy channel of a flexible bronchoscope. Non-coherent light, "random" light output containing mixed frequencies, and radiating in all directions from the source, has also been used experimentally in PDT. Random light sources generally have used powerful, full spectrum light bulbs such as halogen, and lenses to filter random light into a small band of directed light, making it easy to target specific tissues.

To treat endobronchial obstruction, the photosensitizer is first delivered by an IV injection, and after it is allowed to be selectively retained in tumor cells, it is followed by bronchoscopic exposure of the lesion to light. One to two days after PDT, bronchoscopy is repeated, to remove necrotic tissue mechanically and, if necessary, the original site, or other new sites are retreated.

Several developers, among them Miravant Medical Technologies (Santa Barbara, CA), Pharmacyclics (Sunnyvale, CA), and Scotia Pharmaceuticals (London, UK), are evaluating various PDT photosensitizers for numerous cancer indications, including nsclc. However, the recent success of PDT in the treatment of macular degeneration, and its potential applications in cardiovascular disease, has shifted interest among developers away from oncology where PDT has experienced limited commercial success.

Photofrin absorbs 630 nm wavelength light energy and produces a singlet oxygen that destroys the tumor. Photofrin-based PDT (see Exhibit 5) was shown to be effective in palliating endobronchial obstruction from lung cancer with an acceptable safety profile. PDT with Photofrin is a tissue-sparing potentially curative treatment for patients with superficial lung cancer who are not eligible for standard treatment (Lam S, etal, ASCO98, Abs. 1781:463a). Also, although PDT and Nd:YAG appear to have similar mortality and morbidity rates, PDT may be a better choice for the treatment of malignant bronchial obstruction because it is technically easier to use, potentially safer, and does not require general anesthesia.

In two randomized trials, conducted in North America and Europe (The Photodynamic Therapy Lung Cancer Study Group), that compared PDT and thermal Nd:YAG laser ablation for palliation of advanced lung cancer patients with endobronchial obstruction, 211 patients were treated either by IV Photofrin (2 mg/kg), followed 2 days later by the red light application of 200 J/cm of tumor length, or with ND:YAG ablation. A debridement was performed 2 days after PDT light application to remove necrotic tissue. One month after treatment, the objective response rate was higher (55%) with PDT than with laser ablation (30%). Improvement in dyspnea grade was achieved 30% of patients treated with PDT, as compared to only 17% in patients on laser treatment. However, patients on PDT reported more adverse events with regards to photosensitivity reactions (20%), dyspnea (32%), hemoptysis (18%), and bronchitis (11%). Early deaths and overall survival were similar for both treatment arms (Wieman TJ, etal, ASCO98, Abs. 1782:464a).

According to a retrospective review of medical records of 102 patients treated for bronchial obstruction by Nd:YAG laser vaporization (n=83), or by PDT using the tunable dye laser in combination with a light-sensitive dye (n=19), conducted by the University of Louisville School of Medicine (Louisville, KY) between 1988 and 1999, 30-day morbidity and mortality rates were comparable in both groups (22% for Nd:YAG versus 31% for PDT). Equally common complications in both groups were respiratory failure and hypoxemia. Five Nd:YAG patients (6%) died within 30 days after treatment, 3 of respiratory failure and 2 of massive hemoptysis, whereas 2 patients (10%) died in the PDT group, 1 of massive hemoptysis and 1 of acute myocardial infarction (Taber SW, etal, Surgery, Oct 1999;126(4):730-3; discussion 733-5).

Based on a 14-year retrospective review of Photofrin-based PDT, performed on 175 patients (Stage I=16, Stage II=9, Stage IIIa=42, Stage IIIb=64 and Stage IV=44) with endobronchial tumors, conducted at the Grant Laser Center (Columbus, OH) using an argon dye laser system, between 1982 and May 1996, PDT may be considered as an alternative treatment for patients under consideration for surgical treatment for stage I carcinoma in whom the risk of surgery is high. Also, the duration of palliation for patients with incurable disease was equal to or better than that reported historically for most other treatment regimens. The 5-year disease-specific survival of patients with Stage I disease was 93%; the MST in this group had not been reached at the time of this review. MST was 22.5 months in Stage II disease; 5.7 months in Stage IIIa, 55 months in Stage IIIb, and 5.0 months in Stage IV (McCaughan

JS Jr and Williams TE, J Thorac Cardiovasc Surg, Dec 1997;114(6):940-6; discussion 946-7).

A similar conclusion regarding the use of PDT as an alternative to surgery in roentgenographically occult SCC of the lung, was arrived at by investigators at the Mayo Clinic (Jacksonville, FL) after treating 21 patients with 23 cancers with early stage SCC eligible for surgical treatment but offered PDT as an alternative to resection. After an initial PDT session, 15 patients (16 cancers) experienced a CR which lasted more than 12 months in 11 patients (52%), based on a mean duration of follow-up of 68 months (range=24 to 116). Of the original 21 patients, 9 (43%) were spared an operation. On the basis of this clinical trial, it can be concluded that at least 22% of patients with early-stage SCC who are candidates for PDT, can be spared surgery (Cortese DA, etal, Mayo Clin Proc, Jul 1997;72(7):595-602).

Pleurodesis for malignant pleural disease may also be carried out with PDT. In a phase II trial, conducted at the University of Pennsylvania (Philadelphia, PA), pleural PDT was used as part of a multimodality approach in 5 patients with nsclc with malignant pleural spread. The trial endpoint was to determine the effect of PDT on locoregional control when combined with surgery, and conventional chemotherapy/radiotherapy. Four patients with Stage IIIb (T4N2M0) nsclc were treated with chemotherapy to best response, followed by surgical resection of the primary tumor, debulking of the pleural tumor and pleural PDT, and 1 patient was treated with surgery, and PDT alone. Photofrin (2 mg/kg) was administered 24 hours prior to planned surgery, and 30 J/cm^2 of 630 nm light was delivered to the pleura after surgery. Mediastinal radiation (approximately 50 Gy) was delivered postoperatively, if indicated. All patients are alive at a median follow-up of 10 months from the initiation of systemic therapy; 1 patient developed bone metastases 13 months after the initiation of treatment. No Grade 3 or 4 PDT-related toxicities were observed (Friedberg JS, etal, ASCO99, Abs. 1941:503a).

Scientists at the Institute of Biostructure (Warsaw, Poland) observed a potentiation of antitumor effects of Photofrin-based PDT when combined with G-CSF, in two murine tumor models, colon-26 and Lewis lung carcinoma. Also, tumors treated with both agents contained more infiltrating neutrophils, and apoptotic cells, than tumors treated with either agent alone. Importantly, simultaneous administration of Photofrin and G-CSF stimulated bone marrow and spleen myelopoiesis, that resulted in an increased number of neutrophils demonstrating functional characteristics of activation (Golab J, etal, Br J Cancer, Apr 2000;82(8):1485-91).

LumaCare LC-051, a simple non-coherent light source, is currently under *in vitro* studies in lung cancer PDT at the University of Pennsylvania Medical Center (UPMC). MBG Technologies (Newport Beach, CA) and its UK affiliate, Ci-Tec, have developed and own the intellec-tual property rights for the LumaCare lamp, marketed by LumaCare. LumaCare produces noncoherent light within any specific bandwidth in the 350-800 nanometer range, which is suitable for most PDT treatments. Once the photosensitizer is in place, the LumaCare lamp can irradiate target tissues with a fixed frequency light source unique to each photosensitizer and lesion.

The LumaCare lamp is composed of two main components, a base unit, which generates all light in a variable power range, and an applicator, which filters, focuses, and aims light on the target. Applicators are designed for the specific PDT treatment. The device is lightweight, simple to operate, requires little maintenance, and does not need recalibrations. The retail price of the LumaCare LC-051 model ranges from $15,000 to $25,000 per unit. The LC-051 lamp can function as an external or internal PDT activation light and can also be used in non-PDT light activated medical treatments.

PH-10, under development by Photogen Technologies (Knoxville, TN), is a light-sensitive drug that when activated with X-rays, green light or ultra fast-pulsed near-infrared light, has the potential to treat cancer, and certain dermatologic conditions virtually anywhere in or on the body. The drug is indicated for lung cancer as well as breast and prostate cancer, Barrett's esophagus and psoriasis. In laboratory mice, treatment with PH-10 resulted in a 90% kill rate of cancerous tumor cells within 48 hours. In November 1999, Photogen entered into an agreement with Akorn (Buffalo Grove, IL), a manufacturer and marketer of diagnostics and pharmaceuticals, for the latter to develop certain formulations of PH-10. Akorn will develop and document raw materials, production and testing procedures and specifications, necessary for NDA filings.

Hyperthermia

Hyperthermia is being evaluated in numerous oncologic indications (see FO, p 918), including lung cancer and has recently been combined with various chemotherapeutics in the treatment of lung cancer.

A phase I clinical trial (protocol ID: NCI-00-C-0019) of escalating doses of paclitaxel, administered via hyperthermic retrograde isolated lung perfusion in patients with unresectable cytologically confirmed primary lung cancer, or pulmonary metastases, is ongoing, sponsored by the NCI (David S. Schrump, Chair). A maximum of 39 patients, to be accrued for this study, will undergo posterolateral thoracotomy, or median sternotomy, and will be treated with paclitaxel administered via hyperthermic retrograde isolated lung perfusion over 90 minutes. The entire procedure lasts approximately 4 hours. Cohorts of 3-6 patients are being treated with escalating doses of paclitaxel until the maximum tolerated dose (MTD) is determined. Patients are followed monthly. The trial's objectives are to determine the maximum tolerated dose, and phase II dose of paclitaxel, define the nature of the toxic effects of this treatment, evaluate its pharmacokinet-

ic profile and examine the relationship between pharmacodynamic parameters and toxicities.

Another combination involves hyperthermia and liposomal drug delivery. A recent review of the literature indicated that hyperthermia, in combination with a liposomal drug, had an enhanced therapeutic effect compared to either treatment modality alone, or hyperthermia and free drug (Kong G and Dewhirst MW, Int J Hyperthermia, Sep-Oct 1999;15(5):345-70).

BSD-2000/3D System, developed by BSD Medical (Salt Lake City) and funded, in part, by NCI grants, is a new generation of deep regional hyperthermia that uses external three-dimensional focusing of microwave energy to destroy large deep tumors, including lung malignancies. The key component of the BSD-2000 3D System is the Sigma Treatment System that directs the energy from multiple applicators positioned around the patient to generate heat deep within the body to focus the heating pattern to individual tumors. This system includes a treatment base and couch, patient handling system and water cooling system. The deep treatment capability is provided through the use of individual applicators which surround the patient and radiate radiofrequency energy directly into the human body. The BSD-2000 portion of this system has been granted an IDE by the FDA for investigational use as part of an approved clinical study. BSD plans to apply to the FDA for an IDE for the BSD-2000 3D/MR System which is integrated with the MAGNETOM Interventional MR imaging system marketed by Siemens Medical Systems (Iselin, NJ). Clinical research using the integrated hyperthermia-MR system is being conducted under the direction of Professor Rolf Issels, MD, PhD, at Klinikum Grosshadern of the LMU Munich University Medical School (Munich, Germany). Initial clinical use has demonstrated the ability to provide simultaneous heating and noninvasive treatment monitoring using the BSD-2000/3D/MR.

Perfusion-induced systemic hyperthermia (PISH) involves extracoproreal heating of a patient's blood, and removal of toxins for the treatment of nsclc. In February 2000, ViaCirQ (formerly IDT; Pittsburgh, PA), a subsidiary of BICO (formerly Biocontrol Technology; Pittsburgh, PA), obtained FDA approval to continue a human clinical trial at the University of Texas Medical Branch (Galveston, TX), in conjunction with HemoCleanse (Lafayette, IN), to deliver PISH for the treatment of nsclc. PISH uses the ViaCirQ ThermoChem technology which is composed of the ThermoChem-HT System that heats and circulates the blood while maintaining core body temperature, and the ThermoChem-SB System that balances blood chemistries on a "real-time" basis, and removes toxins from the blood. In July 1998, ViaCirQ completed the first phase of an FDA-approved study involving five patients with Stage IV nsclc, in which core body temperature was raised to 42 °C (107.6°F) for two hours by direct extracorporeal heating of the blood. In the follow-on clinical trial, the FDA allowed Stage IIIb patients to be included in the study whose objectives include tumor response, and patient PS, and survival.

The ThermoChem technology for whole body and regional hyperthermia has been under development by IDT since 1992. The ThermoChem-HT System has been cleared for marketing as a intraperitoneal approach to raise the core temperature of the peritoneum to 42 °C by continuous lavage with sterile solution, as part of an operative procedure to treat patients with advanced ovarian, and gastrointestinal cancer.

Cryotherapy

Cryotherapy provides effective and rapid control of symptoms caused by tracheobronchial carcinoma and improves quality of life and survival. It is easy to perform, with minimum complications and the majority of patients are discharged the same day. The procedure may be performed under general or local anesthetic using a rigid or flexible cryoprobe. A temperature of about 70 degrees C is delivered to the tumor site for two 3-minute periods causing destruction of the tumor mass.

In a prospective study of 153 consecutive patients (nsclc=88.2%, sclc=11.1% and malignant melanoma=0.7%) treated at Harefield Hospital (Middlesex, UK), between January 1995 and December 1997, symptoms improved after cryotherapy. At the time of treatment the majority of patients with nsclc had advanced disease (Stage II=8.2%, Stage IIIa=27.4%, Stage IIIb=25.9%, and Stage IV=38.5%). Subjective symptomatic improvement for cough was 68.3%, dyspnea 63.9%, hemoptysis 92.7% and chest pain 55.5%. Respiratory function tests also showed improvement, and PS increased by 54.6%. MST was 12.9 months. Complications occurred in 11 patients (7.2%) but there was no operative mortality (Maiwand MO, Eur J Cardiothorac Surg, Jun 1999;15(6):764-8).

Radiofrequency bronchoscopic surgery with cryotherapy also appears to be a useful technique in the treatment of tracheobronchial obstruction, according to results of a retrospective study of 98 patients, treated at Azienda Ospedaliera San Luigi Gonzaga (Torino, Italy), between January 1994 and June 1995, with this approach, either before (Group 2, n = 48), or after (Group 1, n = 50) radiotherapy and/or chemotherapy. The intervention was considered successful if the lumen was opened by >80%, and partially successful if it was opened by >50%.

In Group 1 treatment was successful in 60%, partially successful in 32%, and unsuccessful in 8%; MST was 5 months from the time of bronchoscopic surgery. In Group 2 treatment was successful in 66%, partially successful in 21.5%, and unsuccessful in 12.5%, with an MST of 14 months from the time of bronchoscopic treatment. A Dumon stent was inserted in 40 patients, 24 in Group 1, and 16 in Group 2 (Marasso A, etal, Thorax, Feb 1998;53(2):106-9).

Stents

Prosthetic endobronchial stents are increasingly used to maintain bronchial patency, both in malignant and in certain nonmalignant diseases. Tracheobronchial stents are often needed in the treatment of obstructions from submucosal or extrabronchial lesions, and represent the only alternative for extraluminal compression. In these situations stents result in effective palliation, and may prolong survival.

Various stent models have been developed for the treatment of inoperable airway stenoses. They consist mainly of metal or silicone (silastic) devices, or combinations of both (hybrid models). The choice of a specific stent depends on the nature of the airway obstruction, the endoscopist's preference, and the cost of the device/procedure. Best results are usually obtained using a combination of stent placement followed by tumor-specific treat-ment such as RT or chemotherapy (Stohr S and Bolliger CT, Monaldi Arch Chest Dis, Jun 1999;54(3):264-8).

Stents are introduced using either a rigid or flexible bronchoscope, and are positioned under direct vision, or with the aid of radiopaque skin markers, fluoroscopy, or a combination of these approaches. Although most available tracheobronchial stents have been shown in various clinical series to achieve immediate resolution of respiratory symptoms from various tracheobronchial obstructions, their long-term effectiveness varies significantly.

Silicone stents are tube-like devices that are usually placed during general anesthesia using a rigid bronchoscope. Among such stents are the:

- Dumon stent, manufactured by Bryan (Woburn. MA), constructed of molded silicone with regularly placed studs on its external surface to reduce displacement, this device has been available since the early 1960s but is not popular today because insertion requires use of a rigid bronchoscope under general anesthesia
- Polyflex prototype stent, developed by Rüsch (Kernen, Germany), constructed of silicon with a polyester mesh, that shows promise, although there is no sufficient follow-up data to date to draw final conclusions
- Harrell Y stent, a silicone stent supplied by Hood Laboratories (Pembroke, MA) that is used in cases of distal tracheal or carinal lesions

Expandable metal stents can be safely inserted under local anesthesia by flexible bronchoscopy, resulting in improved symptoms and pulmonary function in patients with malignant airways obstruction (Wilson GE, etal, Thorax 1996, 51(3): 248-252). Metal stents can be combined with other palliative treatments such as chemotherapy, laser therapy, and external or endobronchial RT. Bare metal stents rapidly become epithelized and incorporated into the bronchial wall, with cellular covering being visible by the third week, allowing normal mucociliary clearance to occur. However, if a wire stent is placed overlying a lobar orifice, this area does not become epithelized, thus preventing occlusion of the lobar bronchi.

Among metallic stents, the following have been evaluated in endobronchial applications:

- Wallstent, manufactured by Boston Scientific's (Boston, MA) Microvasive Division, is composed of filaments of a cobalt-based alloy braided in the form of a tubular mesh; because of the absence of hooks, and a reduced strut pressure, migration rates associated with Wallstent were higher (22%-83%) than those of the Gianturco stent (0%-4%) in malignant disease; Wallstent is covered by Permalume, a polyurethane coating, and is inserted using the Unistep Plus reconstrainable delivery system
- Gianturco-Rösch Cook-Z tracheobronchial stent, manufactured by Cook (Bloomington, IN), is constructedfrom a continuous loop of stainless steel in a double coil format of zig zag wire and also comes with a silicone covering; the proximal and distal extremities of the wire have small hooks that anchor into the airway wall; because of its design this stent exerts greater strut pressure on airway walls than the Wallstent
- Ultraflex, also supplied by Microvasive, is a covered tracheobronchial stent, constructed from nitinol, that exerts constant pressure to maintain patency
- Palmaz stent, manufactured by Cordis (Miami, FL), a Johnson & Johnson business unit, has also been successfully used in tracheobronchial obstructive lesions (Beer M, etal, Cardiovasc Intervent Radiol 1999;22:109-113), but generally this stent exhibits a high clinical short-term success rate but a low long-term success rate (>7 days), predominantly because of stent obstruction, encrustment, tumor penetration and pneumonia
- Strecker Stent, a variation of an arterial stent also manufactured by Cordis, is constructed of loosely connected loops of single tantalum filament that allow the stent to have elastic properties; one of its unique features is that, unlike other stents, it can be compressed in the radial as well as the longitudinal direction, and it is flexible in the compressed state as well as in the dilated state

Common complications of metallic stents include migration, obstruction, encrustment, tumor penetration and, rarely, vascular and airway perforation. Because, theoretically, tumors can grow through the metal latticework of bare metal stents, and reocclude the airway, bare metal stent use is more appropriate in extraluminal tumor compression, and covered metal stents in intraluminal tumors. However, covered metal stents may interfere with the normal mucociliary clearance mechanisms. Stents like the Gianturco because of increased strut pressures and anchoring hooks is less likely to migrate than the Wallstent, but is more likely to cause airway or vascular perforation.

Presently, there is no ideal stent because none is free of complications and none are able to consistently maintain life-long patency. Gianturco stents are associated with serious major complications such as bronchial perforations, strut fractures and migration (Nakajima Y, etal, Cardiovasc Intervent Radiol, Jul-Aug 1999;22(4):287-92) and are no longer recommended for use in the tracheobronchial tree. The Palmaz stent has also fallen into disfavor, because a strong external force, such as a vigorous cough, can recompress it. The Strecker stent can only be used in smaller airways, but may be useful in the accurate stenting of short segment stenoses because it does not foreshorten on deployment. The Wallstent and Ultraflex stents are the metallic stents of choice at the Cleveland Clinic Foundation, in Ohio. Both are easy to deploy, available in covered forms, exert adequate radial force, remain relatively stable in position, and have good longitudinal flexibility for use in tortuous airways. Disadvantages include excessive tissue formation, and difficulty in removing the stent once it has been epithelialized. Potential new developments include removable metallic stents, biodegradable stents, and chemically and radioactively coated stents (Rafanan AL and Mehta AC, Radiol Clin North Am, Mar 2000;38(2):395-408).

The safety, efficacy, and tolerance of the covered Wallstent, inserted either by a rigid bronchoscope, or a flexible delivery system, was investigated in an 8-month prospective multicenter study for the palliative treatment of 40 patients with inoperable tracheobronchial cancer at four teaching hospitals in Switzerland and Germany. After partial airway recanalization with an Nd-YAG laser, the covered Wallstent was inserted 23 times using a rigid bronchoscope and 27 times using a flexible delivery system under fluoroscopic, and endoscopic visualization. Clinical and endoscopic examination at 1, 30, and 90 days showed improvement in the bronchial lumen, and in the dyspnea index. No serious complications (death, perforation, hemorrhage, inability to remove an improperly placed prosthesis) was observed during surgery. Late complications included migration (12%), inflammatory granulation, or tumor regrowth at the tip of the prosthesis (36%), and symptomatic retention of secretion (38%). Compared with other tracheobronchial prostheses, notably the Dumon stent, the covered Wallstent had the following advantages, insertion with visual guidance, treatment of extrinsic compressions, and esophagobronchial fistulas, and little chance of migration when the prosthesis diameter was chosen correctly; disadvantages included a high price, difficulty in repositioning and extraction of the released stent, and risk of granulations at the tips of the prosthesis and retention of secretions (Monnier P, etal, Chest 1996; 110:1161-68).

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