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NEW APPROACHES FOR THE TREATMENT OF HEAD AND NECK CANCER
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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

HEAD AND NECK CANCER — PART II DIAGNOSIS, STAGING, PROGNOSIS, AND TREATMENT

Major advances have been made in the last few decades in the diagnosis, staging and treatment of head and neck squamous cell carcinoma (HNSCC). Progress in imaging techniques as well as molecular biology, has aided understanding of the natural history of HNSCC and allowed for more accurate staging of this often disabling malignancy. Advances in surgical technique and radiotherapy, the treatment mainstay for early HNSCC, are being augmented by new chemotherapeutic approaches that address disease at later stages. However, although response rates to chemotherapy have increased, there has not been an appreciable advance in extending survival.

Despite disappointing results in many chemotherapy trials, HNSCC has served as a paradigm for broader oncologic principles of minimizing toxicity of therapy to achieve similar results with less morbidity. Clinical trials in progress, focusing on multimodality approaches and on novel therapeutic agents, also appear to be producing more favorable results.

DIAGNOSIS, SCREENING AND STAGING

Because head and neck cancer encompasses a heterogeneous group of malignancies, it is impossible to completely generalize its diagnosis and staging. Some principles hold true, however, that are helpful when approaching these tumors clinically. To begin with, although there are many histologic subtypes, the vast majority (95%) are squamous cell tumors and this review will assume that all references reflect this type of cancer unless specifically noted. HNSCC is commonly further defined as oropharyngeal and oral cavity cancer.

Diagnosis of HNSCC is focused on identifying primary lesions and assessing extent of involvement of adjacent and distant organs. The staging system currently employed varies from site to site but follows the typical TNM classification (see Exhibit 1 for the general schema). In general, tumor (T) designation varies from site to site but the terminology corresponds to increasing size of primary tumor (T1-T3) and involvement of adjacent structures. The nodal (N) designation is similar for all sites. Because outcome is so clearly related to extent of disease (i.e., stage), it is crucial that HNSCC is diagnosed as early and as possible and staged accurately. For example, in patients with N0 or N1 disease there is only a 10% risk of presence of distant metastases (Vokes EE, etal, NEJM 1993; 328;184-94).

Treatment options and survival outlook depend on disease stage at initial diagnosis. Approximately 65% of patients present with regionally or distantly advanced disease at time of diagnosis in the USA (see Exhibit 2). Based on SEER data from the 1973-1992 period, the 5-year survival rate for HNSCC is 41.6% when it has spread regionally and 18.3% for distant disease (see Exhibits 3 and 4). Other more recent statistics estimate the 5-year survival rate for HNSCC that spread beyond the local site, at 25% to 35% (see Exhibit 1).

Many HNSCC patients present with signs and symptoms that are specific to the site of involvement and easily misdiagnosed. For example, patients with malignancies of the sinuses may be misdiagnosed with sinusitis and, thus, treated unsuccessfully with antibiotics for a prolonged period. A thorough history and physical exam, with attention to the head and neck area, is imperative. The oral cavity is easily inspected and may show signs of both leukoplakia and erythroplakia. Because these are precursors to frank malignancy, any suspicious lesions are biopsied to further define their malignant potential. A systematic examination of the lymph nodes of the head and neck is performed to assess extent of disease as well as to determine the location of a biopsy site that may be necessary to establish a diagnosis.

Once diagnosed, appropriate staging is performed that is somewhat site-specific. In general, imaging studies such as a panoramic x-ray of the mandible and CT scanning of the head and neck, are performed to assess extent of local disease. Suspicious lymph nodes may require biopsy. A chest x-ray is generally obtained on all patients as the lung is the most common site of distant spread. If a patient relapses, complete restaging must be done in order to select the next appropriate therapy (McGuirt WF, Laryngoscope 1982; 92(5):569-576; NIH Conference, JAMA, 1988; 259(14):2132-2138).

Initial diagnosis of cancers of the oral cavity and pharynx includes an endoscopy (under general anesthesia) and a biopsy for definition and histopathologic confirmation of the lesion as malignant. The appropriate nodal

drainage areas are examined by careful palpation. A flexible laryngoscope is used to view the larynx. India ink is used to tattoo lesions in the oral cavity for the purpose of identification in future surgical procedures.

Panendoscopy

The role of panendoscopy (direct laryngoscopy, bronchoscopy and esophogoscopy) is somewhat controversial. Technically, this is a screening procedure performed on patients already diagnosed with some type of head and neck cancer to look for other primary tumors. Because patients are at increased risk for synchronous and metachronous lesions, it is hoped that panendoscopy will reveal lesions that are amenable to curative intervention. The risk of developing a second malignancy in HNSCC has been confirmed and occurs at a rate of approximately 4% per year (Lancet 1981; 2:547). However, the likelihood of discovering a second malignancy at the time of diagnosis of the index case by panendoscopy is 10% (Arch Otolaryngol 1985; 11 1:589).

Exhibit I
TNM Staging System for Head and Neck Cancer

	Tumor Staging	
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Carcinoma *in situ*	
T1	Tumor ≥2 cm in greatest dimension	
T2	Tumor >2 cm but < 4 cm in greatest dimension	
T3	Tumor > 4 cm in greatest dimension	
T4	Tumor invades adjacent structures (eg, cortical bone, soft tissues of neck, deep muscle of tongue, maxillary sinus, skin)	
	Lymph Node Staging	
NX	Regional lymph nodes cannot be assessed	
N0	No regional node metastases	
N1	Metastasis to a single ipsilateral lymph node (>3 cm)	
N2	Metastasis to a single ipsilateral lymph node (> 3 cm but < 6 cm), to multiple ipsilateral lymph nodes (none > 6 cm), or to bilateral or contralateral lymph nodes (none > 6 cm)	
	a Metastasis to a single ipsilateral lymph node (> 3 cm but < 6 cm)	
	b Metastases to multiple ipsilateral lymph nodes (none > 6 cm)	
	c Metastases to bilateral or contralateral lymph nodes (none > 6 cm)	
N3	Metastasis to a lymph node > 6 cm	
	Metastasis Staging	
MX	Presence of distant metastasis cannot be assessed	
M0	No evidence of distant metastasis	
M1	Distant metastasis	
Clinical Staging		***5-Year Survival Rate (%)***
0	Tis N0 M0	93-95
I	T1 N0 M0	90-92
II	T2 N0 M0	75-85
III	T3 N0 M0; T1 N0 M0	50
IV	T4 N0-1 M0; any T N2-3 M0; any T and N M1	25-35

Stages are defined by TNM classification (American Joint Committee on Cancer: Manual for Staging of Cancer. Philadelphia: JB Lippincott Company, 3rd ed., 1988, 33-38).

Non-invasive Imaging

In assessing primary tumor size and metastasis to the lymph nodes, MRIs were shown to be more beneficial than CT scans. Liver, spleen, nor bone scans have been found to be of significant diagnostic value. Optional assessment of the bronchi is most effective using a chest x-ray. Angiography, cine pharyngoesophagogram, and other tests are also used when indicated (McGuirt WF, NIH Conference, ibid).

In vitro Tests

Curently, there are no commercialized *in vitro* diagnostic tests for HNSCC. This may change as more is known about the molecular basis of oral cancer but, as things stand now, despite numerous advances in the fields of epidemiology and etiology, progress in this area has been slow. HNSCC offers a unique paradigm in identifying molecular markers because of the usual presence of premalignant and malignant stages that allow researchers to identify and compare the role of suspected oncogene abnormalities, such as the amplification of three or more types of these genes, present in these stages, in the development of neoplasia (Pillai R, etal, J Surg Oncol 1991; 47:102-8). Another interesting *in vitro* diagnostic diagnostic approach is detection of viral infections often associated with HNSCC.

Human papillomavirus (HPV) infection of the oral mucosa has been associated with neoplastic changes. Therefore, it appears that a relationship exists between HPV infection and development of oral cavity squamous cell tumors, similarly to the proven association in cervical cancer. However, although the role of HPV and

other viruses in malignant transformation of infected cells has not been fully elucidated, testing for presence of HPV infection may provide an early screening approach to HNSCC. HPV genomes 16, 18, 31, 33, and 35 are considered oncogenic and may be a sensitive marker for prognosis of primary benign lesions. Patients whose biopsies confirm HPV, present in 87% of oral papillomas, may need to be followed-up to prevent subsequent tumor development. Considering the similarities between oral and cervical oncogenesis, HPV induced changes which occur in the cervix, may also occur in oral carcinogenesis (Lakshmi S, etal, J Surg Oncol 1993; 52:193-6).

Exhibit 2
Estimated Stage Distribution of Oral Cavity and Pharynx Cancer at Time of Diagnosis by Gender in the USA 1997

Stage	Male		Female		Total	
	(#)	(%)	(#)	(%)	(#)	(%)
Localized	7,106	34.0	3,940	40.0	11,070	36.0
Regional	9,196	44.0	4,137	42.0	13,223	43.0
Distant	2,090	10.0	788	8.0	2,768	9.0
Unstaged	2,508	12.0	985	10.0	3,690	12.0
All Stages	20,900	100.0	9,850	100.0	30,750	100.0

Source: Based on SEER Cancer Statistics Review, 1973-1992.

Etiology of juvenile and adult laryngeal papillomas (JLP and ALP) and oral papillomas (OP) is associated with HPV infection. Because these benign lesions can undergo malignant conversion, a marker is needed to distinguish progressive from regressive lesions. In a study to detect HPV in papillomas, HPV 6/11 was detected in all JLP (17 of 17), in all ALP (27 of 27), in 13 of 15 (87%) OP, and in seven of 11 (63%) cases of laryngeal leukoplakia (LL). HPV 16, 18, and 33 were detected in six of 27 (22%) ALP, in three of 15 (20%) OP, and in four of 11 (36%) LL. The dominant type was HPV 16; HPV 31 and 35 were not detectable. Three ALP, one OP, and the four LL cases with oncogene HPV exhibited histologic features of moderate dysplasia. It may, therefore, be prudent to manage patients with positive biopsies confirming HPV 16, 18, or 33 with special care to prevent development of a carcinoma (Arndt O, etal, Laryngo-Rhino-Otologie, 1997 Mar, 76(3):142-9).

Among 187 consecutive patients with HNSCC, overall prevalence of HPV infection was 10.7% and prevalence in nonsmokers was 5%, representing 50% of all infected subjects. This represented a 50% incidence of HPV in nonsmokers that differed significantly from the 8.5% incidence in smokers. HPV occurred more frequently in oropharyngeal squamous cell carcinoma (18.6%) than in other locations (6.1%). None of these patients had p53 gene mutations in cancer cells. These findings suggest that HPV may play a role in HNSCC in nonsmokers (Fouret P, etal, Archives of Otolaryngology, Head and Neck Surgery, 1997 May, 123(5):513-6).

Epstein-Barr virus (EBV) infection has also been shown to be associated with the development of nasopharyngeal carcinoma (see FO, p 610). Cortecs International (London, UK), a public company that specializes in the development of new oral pharmaceutical delivery systems, new oral mucosal vaccines, and point-of-care rapid diagnostics, signed an exclusive agreement in December 1996 with Cancer Research Campaign Technology (CRCT, London, UK) to develop diagnostic tests for nasopharyngeal cancer (NPC). Cortecs plans to initiate a program aimed at developing and commercializing a series of NPC diagnostic products, using whole blood, plasma, serum or saliva. According to the agreement, CRCT will provide access to CRC-funded work by Dr. John Arrand at the Paterson Institute of Cancer Research (Manchester, UK) that has produced reagents and antigens demonstrated to be of use in diagnosing NPC. Cortecs will combine this know-how and technology with its own enzyme-linked immunosorbent assay (ELISA) and rapid point-of-care technologies used in its Helisal range of products, to design an ELISA test for use in hospitals and laboratories in diagnostic screening procedures. The rapid point-of-care tests are planned to be small, self contained and capable of being used without the need for special training or personnel or any additional apparatus and, therefore, may be useful for testing "at risk" populations. The test is based on the finding that NPC patients show an abnormal response to EBV infection. CRCT developed technology which may make it possible to identify patients showing this response.

Telomerase, a ribonucleoprotein that maintains telomere length and whose activity is associated with escape from cellular senescence, may also prove diagnostic in HNSCC. Telomerase was detected in 26 of 35 (80%) primary, fresh HNSCC specimens and in 3 of 6 (50%) head and neck squamous dysplastic lesions using a modified PCR-based assay. In addition, 14 of 44 (32%) oral rinses from a separate group of HNSCC patients contained detectable telomerase activity, whereas only 1 of 22 (5%) oral rinses from controls exhibited such activity. Telomerase activity in oral rinses was compared with corresponding activity in paired primary tumor samples. Seven of the 19 cases demonstrated activity in both tumor and oral rinse, 2 lacked activity in both tumor and oral rinse, 10 demonstrated activity that could not be detected in corresponding oral rinses, and there were no cases of positive oral rinses with corresponding negative tumors. Although limited in sensitivity, this study showed

Exhibit 3
Estimated Five Year Survival Rates of Oral Cavity and Pharynx Cancer by Gender in the USA, 1997

Stage	Males			Females			Total		
	Incidence	5-Year Survival		Incidence	5-Year Survival		Incidence	5-Year Survival	
	(#)	(#)	(%)	(#)	(#)	(%)	(#)	(#)	(%)
Localized	7,106	5,607	78.9	3,940	3,286	83.4	11,070	8,911	80.5
Regional	9,196	3,568	38.8	4,137	1,973	47.7	13,223	5,501	41.6
Distant	2,090	345	16.5	788	182	23.1	2,768	506	18.3
Unstaged	2,508	680	27.1	985	485	49.2	3,690	1,214	32.9
All Stages	20,900	10,116	48.4	9,850	5,930	60.2	30,750	16,021	52.1

Source: Based on SEER Cancer Statistics Review, 1973-1992.

that telomerase activity analysis in oral rinses represents a novel method to detect presence of cancer cells shed in the upper aerodigestive tract (Califano J, etal, Cancer Research, 1996 Dec 15, 56(24):5720-2).

Cytology

Unlike the success and widespread use of exfoliative cytology (Pap smears) in the screening for cervical cancer, such an approach has not met with equal success in screening for cancer of the oral cavity. Although application of new quantitative and immunocytochemical techniques has refined the potential role of this approach, lack of a marker present only in malignant lesions, has limited its clinical utility in HNSCC. In order to use exfoliative cytology in HNSCC, several markers whose sensitivity and specificity have not been categorically determined, must be identified simultaneously to provide diagnostic information. Such an approach is not feasible for screening applications. Currently, oral exfoliative cytology may prove more useful in providing DNA samples from biopsy-proven oral cancers that can be evaluated to identify any mutations that may be prognostic and also predict response to therapy (Ogden GR, Oral Oncol, 1997 Jan, 33(1):2-4).

Biological Staging

Biological staging of tumor progression in oral mucosa may be accomplished by multi-marker detection and may result in early detection of premalignant and malignant HNSCC lesions. Expression patterns of various markers such as cytokeratin protein types 10/11, 13, 16, 19, 18, 14 and pancytokeratin, involucrin, ras, p21, epidermal growth factor (EGF) and its receptor (EGFr), were assessed immunohistochemically in various stages of tumor progression in oral mucosa. Expression patterns of cytokeratin types 10/11, 14 and 19, involucrin and EGFr were significantly correlated with tumor progression in oral mucosa in both univariate and multivariate analysis. Biological staging of a lesion may be more useful in assessing the stage of tumor progression in oral mucosa than histopathologic grading (Kannan S, etal, International Journal of Biological Markers, 1996 Apr-Jun, 11(2):67-76).

PROGNOSIS

Various factors such as patient health status, tumor attributes and treatment choices, play a role in HNSCC prognosis. Patient factors are particularly relevant in many HNSCC cases because prognosis is often hampered by the presence of comorbid illnesses that impact on treatment choice and outcome. Such illnesses, usually related to tobacco and alcohol abuse, lower a patient's performance status independent of any malignancy. In fact, it has been estimated that fully 30% of the deaths in this group of patients is attributable to comorbid illnesses and not the malignancy itself (NEJM 1993;328:184).

Factors such as clinical stage, resectability, and depth of invasion, also affect patient outcome. Among tumor factors, the most significant indicator of prognosis seems to be pathological nodal stage.

Increasingly, biological phenotypes of cancer cells are being used to predict effects of cancer treatment and clinical course. Predictive factors of survival include DNA ploidy, potential doubling time (Tpot), EGFr and cyclin D1. C-erbB-2 and p53 do not appear to predict survival of patients with HNSCC (Horiuchi M, Gan To Kagaku Ryoho Japanese Journal of Cancer and Chemotherapy, 1996 Feb, 23(3):257-64).

p53

Among markers with prognostic value in HNSCC, p53 gene has been investigated most extensively and, although some of the findings are contradictory, it appears that this tumor suppressor gene is a significant prognostic factor in HNSCC. It was originally determined that derangements of p53 confer a poor prognosis (Brahman DG, Semin Oncol, 1994 Gun, 21(3):320-9). Expression of p53 protein in primary HNSCC was predictive of shorter survival because of its association with earlier

Exhibit 4
Estimated Five Year Survival Rates for Oral Cavity and Pharynx Cancer in Major World Regions, 1997

	North America			Europe*			Triad			Total Selected World Regions		
Stage	Incidence	5-Year Survival		Incidence	5-Year Survival		Incidence	5-Year Survival		Incidence	5-Year Survival	
	(#)	(#)	(%)	(#)	(#)	(%)	(#)	(#)	(%)	(#)	(#)	(%)
Localized	12,182	9,807	80.5	19,630	14,742	75.1	33,785	26,285	77.8	150,714	119,064	79.0
Regional	14,551	5,529	38.0	23,447	5,674	24.2	40,355	12,550	31.1	180,019	55,986	31.1
Distant	3,046	521	17.1	4,907	476	9.7	8,446	1,132	13.4	37,678	5,087	13.5
Unstaged	4,061	1,226	30.2	6,543	1,309	20.0	11,262	2,827	25.1	50,238	12,660	25.2
All Stages	33,840	17,191	50.8	54,527	21,756	39.9	93,848	42,560	45.4	418,649	192,788	46.1

**Excluding the former USSR*

development of both tumor recurrence and second primary tumors. Among 90 patients with HNSCC, p53 protein was detected in 50%. Prevalence of metastasis was higher in patients with p53-positive tumors; also p53 expression was closely correlated with survival time and may, therefore, be useful as a prognostic parameter in HNSCC (Takano I, etal, Nippon Jibiinkoka Gakkai Kaiho J Oto-Rhino-Laryngological Society of Japan, 1997 May, 100(5):524-33). Furthermore, p53 expression may serve as a means of identifying individuals at high risk of recurrent primary disease and second primary tumors that may benefit from adjuvant therapy and chemoprevention after definitive local therapy (Shin DM, etal, Journal of the National Cancer Institute, 1996 Apr 17, 88(8):519-29).

Although p53 and retinoblastoma (Rb) inactivation are commonly found in HNSCC, alterations at either p53 or Rb are only weakly associated with tumor aggressiveness. However, in many cancers loss of heterozygosity (LOH) at multiple loci is associated with decreased survival. Using PCR and highly informative microsatellite markers, DNA from matched sets of 63 HNSCC and normal tissues was compared for LOH at the p53 and Rb loci. At p53, 50 were informative, with LOH occurring in 19 (38%). Of the 57 that were informative at Rb, LOH occurred in 21 (37%). Of the 46 that were informative at both p53 and Rb, LOH at both loci occurred in 10 (22%). Although no correlation was found when LOH for p53 or Rb was compared to stage, differentiation, and survival, LOH at both loci predicted a significantly poorer survival. This strongly supports the contention that simultaneous alterations of these two tumor suppressor genes favors tumor aggressiveness and can be used as a prognostic indicator (Gleich LL, etal, Laryngoscope, 1996 Nov, 106(11):1378-81).

Serum antibodies to p53 were recently reported as a marker that might be useful in identifying patients with a high probability of failure when treated with conventional therapies (Bourhis J, etal, ASCO96, Abs. 899:317). Using ELISA, incidence of p53 antibodies in the serum was investigated in 143 HNSCC patients. Of these, 39 (27.3%) were seropositive for p53 antibodies. The post-therapy course of two matched study groups, one consisting of 38 p53-antibody-seropositive patients and the other of 38 p53-antibody-seronegative ones, was followed-up for 24 months. During this period, p53-antibody-seropositive patients accounted for more local tumor recurrences (12 versus 8) and more tumor-related deaths (5 versus 1) than did seronegative patients; also, second primary tumors occurred exclusively in seropositive patients (9 versus none). Overall, therapy failures (recurrences, tumor-related deaths, second primaries) were observed in 17/38 (44.7%) p53-antibody-seropositive cases and in 8/38 (21.1%) of p53-antibody-seronegative cases. These results, after a follow-up of 2 years, seem to indicate a prognostic value of p53 serum antibodies for therapy failure in patients with HNSCC (Werner JA, etal, Cancer Immunology, Immunotherapy, 1997 Apr, 44(2):112-6).

Prediction of sensitivity of tumor cells to radiation may be another role for p53. A study undertaken to establish an association between mutations in p53 and radiotherapy outcome, found a remarkable variation in radiosensitivity among 16 cell lines from oral cavity carcinomas. Eleven of 16 cell lines with a mutated p53 gene were significantly more radiation sensitive than those with wild type (wt) p53 (AUC 1.9 +/- 0.2 Gy and 2.3 +/- 0.2 Gy, respectively). However, structural alterations in the p53 gene were also observed in three of relatively resistant cell lines, which indicates that not all mutations are critical in this respect (Pekkola-Heino K, etal, Acta Oto-Laryngologica, 1996 Mar, 116(2):341-4). For instance, radiation-resistant HNSCC line JSQ-3 carries a mutant form of p53. Treatment of these cells with an adenoviral vector containing wtp53 (Av1p53) inhibited their growth *in vitro* and *in vivo* but had no effect on normal cells. More significantly, introduction of wtp53 also reduced the radiation-resistance level of this cell line *in vitro*, in a viral dose-dependent manner. Furthermore, this radiosensitization was also observed *in vivo*. Complete, long-term regression of JSQ-3 cell-induced mouse xenografts for up to 162 days was observed when a single

dose of Av1p53 was administered in combination with ionizing radiation, demonstrating the effectiveness of this combination of gene therapy and conventional radiotherapy. (Pirollo KF, etal, Oncogene, 1997 Apr 10, 14(14):1735-46).

Exhibit 5
Correlation of Selected Growth Factor Expression and Survival in HNSCC

Growth Factor	Expression Level			
	Group 1 (15 samples)	Group 2 (18 samples)	Group 3 (7 samples)	Group 4 (3 samples)
EGFr	none	10	50	100
TGF-α	none	none	none	expressed
	Mean Survival			
	27 months	23 months	34 months	10 months

Because the high local recurrence rate associated with HNSCC is attributable to incomplete tumor resection, use of molecular markers may prove a more accurate means of establishing surgical margins and, thus, reducing the incidence of such recurrence. Currrently, surgical margins are determined by histopathology of frozen sections. However, because it is believed that genetic and molecular changes precede gross histologic alterations, tumor markers may provide a more accurate means of defining surgical margins. For instance, definition of surgical margins, based on p53 positivity, may prove to be a more sensitive marker in patients who were deemed to have negative margins by traditional light microscopy (Brennan JA, etal, NEJM, 1995 Feb 16, 332(7):429-35).

Growth Factors

Incidence of TGF-α and EGFr overexpression in 43 patients with tumors of the head and neck was analyzed using molecular biological techniques and expression data was correlated with disease course within a 4-year follow-up period. Tumors were classified into four groups according to EGFr status as shown in Exhibit 5.

There was a significant correlation with EGFr/TGF-α overexpression in group 4 and survival, compared with group 3 and group 1; those who expressed EGFr as well as TGF-α had the poorest prognosis. Increased production of TGF-α and EGFr in tumors of the head and neck may serve both as a marker for tumor progression and as a target for therapy involving inhibition of the autocrine loop or blockage of TGF-α binding (Issing WJ, etal, Anticancer Research, 1996 Jan-Feb, 16(1):283-8).

Cyclin D1

Overexpression of cyclin D1 may be associated with a poor prognosis in HNSCC. Overexpression of cyclin D1 protein was found in 49% of tumors obtained from a well-characterized series of 115 patients with resectable HNSCC at the Netherlands Cancer Institute in Amsterdam. This overexpression was not associated with known prognostic factors such as T and N stages. Tumors recurred more frequently and within a shorter period in those whose primary tumors overexpressed cyclin D1 protein. Overexpression of p53, that was found in 42% of the patients, was of no prognostic significance (Michalides RJ, etal, Head and Neck Surgery, 1997 May, 123(5):497-502). For more information about the cell cycle in malignancy (see FO, pp 591-600).

Eukaryotic Initiation Factor 4E

Eukaryotic initiation factor 4E (eIF4E) may also prove to be a useful tool in establishing surgical margins in HNSCC. For instance, this marker was found to be elevated in all 26 HNSCC samples tested, in contrast to low expression in benign lesions. When surgical margins were analyzed for eIF4E in 23 patients, 12 showed elevated eIF4E in histologically negative margins. Cancer recurred in 5 of these 12 patients as opposed to none of the 11 patients whose surgical margins did not express eIF4E. Therefore, eIF4E may be a sensitive and specific marker for HNSCC, with potential for defining clear resection margins. Correlation between elevated levels of eIF4E at the margins and recurrence confirms its ability to detect malignant cells prior to clear-cut alterations in morphology. The accuracy and simplicity of these assays underscore the usefulness of eIF4E in managing HNSCC (Nathan CA, etal, Oncogene, 1997 Jul 31, 15(5):579-84).

HPV Infection

Presence of HPV infection may also be used as a prognostic factor. In a study to assess their prognostic value, HPV genomes were detected in 9 of 90 patients (10.0%) with HNSCC; tumors of 8 (29.6%) of 9 patients with mesopharyngeal cancer and one (6.7%) with maxillary cancer contained HPV DNA sequences. Almost all HPV infections occurred in patients with mesopharyngeal cancer, and it has been suggested that this anatomic subsite may be more frequently infected by HPV than other sites within the head and neck region. Among the 27 patients with mesopharyngeal cancer, HPV DNA+ patients experienced a higher incidence of CR than HPV DNA- patients (87.5% versus 26.3%) (Takano I, etal, ibid).

Multiple Markers

In a study undertaken to investigate the role of multiple markers, immunohistochemistry was performed on biopsies from 101 HNSCC patients treated by radical radiotherapy, to assess expression of p53, ki-67, c-erbB-2, heat-shock protein-27 (hsp27), and glutathione S trans-

Exhibit 6
Estimated Chemotherapy Treatment Regimens for Head and Neck Cancer in Selected World Regions in 1997

Populations	North America		Europe*		Japan		Triad*	
	(#)	(%)	(#)	(%)	(#)	(%)	(#)	(%)
Incidence of HNSCC	33,840	100.0	54,527	100.0	5,481	100.0	93,848	100.0
Total 5-year survival	17,083	50.5	22,201	40.7	3,510	64.0	42,794	45.6
Primary chemotherapy cases	20,318	60.0	32,738	60.0	3,291	60.0	56,346	60.0
Total deaths	9,510	18.9	23,031	37.8	2,371	31.3	34,912	29.3
First relapse cases	7,968	15.8	9,638	15.8	1,195	15.8	18,801	15.8
Second relapse cases	3,530	7.0	4,270	7.0	530	7.0	8,330	7.0
Third relapse cases	303	0.6	366	0.6	45	0.6	714	0.6
Total chemotherapy cases	32,119		47,012		5,061		84,191	

**Excluding the Former USSR*

Source: Estimated relapse and survival rates are derived from published results of population-based head and neck cancer studies

ferase-pi (GST-pi). Expression of each marker was correlated with local control and survival. Tumors of low cell proliferation expressing p53 did not respond to radiation. Relative risk (RR) of radiation resistance of patients with p53-expressing tumors was 3.78 as compared with p53-negative tumors. For tumors with a high growth fraction (ki-67 >20%), the RR was 0.25 compared with tumors with a low growth fraction (ki-67 <20%). When p53 expression and cell proliferation were considered simultaneously, the association with resistance to radiation was significant. The RR for resistance with one (p53 staining or ki-67 <20%) or two (p53 staining and ki-67 <20%) unfavorable markers was 3.8 and 14.87, respectively. There was a strong probability that patients whose tumor expressed p53 with low growth fraction (ki-67 <20%) would not respond to radiation therapy. Absence of p53 expression coupled with a high cell proliferation predicted an excellent outcome after radiotherapy even for patients with advanced disease (Raybaud-Diogene H, etal, Journal of Clinical Oncology, 1997 Mar, 15(3):1030-8).

Apoptotic and mitotic index, DNA index, ratio of cells in S phase, p53 protein overexpression in untreated tumors as well as the changes of these parameters after the first 2 Gy irradiation, except proliferative kinetics parameters, were examined in 15 patients with head and neck carcinoma treated with radiation (14-70 Gy telecobalt), in order to determine the prognostic value of these factors. Inducibility of apoptosis is very low in head and neck carcinomas which correlates with the unfavorable prognosis. The decrease in mitotic index after the first 2 Gy irradiation, which occurred in 7 cases (5 of them alive at the time of reporting), indicates a better chance for relatively longer survival. Aneuploidy and elevated S-phase rate were frequently found in immunohistochemically p53+ tumors (Kraxner H, etal, Acta Oto-Laryngologica, Supplement, 1997, 527:145-9).

TREATMENT OPTIONS BY SITE OF CANCER

Treatment options for HNSCC are diverse and dependent upon disease site and stage. However, a number of generalities apply. Surgery and radiation therapy remain the mainstay of curative treatment, with chemotherapy traditionally used either palliatively or as a predictive tool to stratify patients for organ preserving strategies. Patients with Stage I/II HNSCC are managed with curative intent, typically with surgery and/or radiation therapy. The cure rates in Stage I and II disease are 80% and 60%, respectively. Patients who present with more advanced disease have much poorer outcomes and are generally treated with a combination of surgery followed by radiation therapy in an effort to improve local/regional control. Unlike in earlier stage disease, the majority of these patients will die of persistent or recurrent disease (NEJM 1993;328:184).

While attempting to get rid of a malignant tumor of the head and neck, it is important to preserve form and function and prevent a second primary carcinoma. However, treatment of the initial primary cancer often results in major decline in quality of life. Reconstructive surgery and rehabilitation following pharyngectomy, glossectomy, or composite resection, often cannot completely rectify the potentially extensive cosmetic and functional disabilities.

Prevention of second primary tumors includes careful medical follow-up and programs to encourage cessation of tobacco and alcohol use. The survival rate of patients with a second primary tumor is substantially lower than that associated with the original primary tumor.

The goal in the treatment of oral cavity cancer emphasizes preservation or restoration of mastication and swallowing as well as clarity of speech. Particular care is taken in the resection of the anterior mandible to allow chewing continuity. Tumors involving the hypopharynx and larynx pose particular threat to a patient's ability

to speak and swallow. Tumors of the nasal cavity and paranasal sinuses may cause significant functional and sensory dysfunction. Thus, reconstructive surgery is extremely important in the treatment of cancers of the head and neck.

Oral Cavity and Oropharynx

Oral cavity cancers discovered at an early stage, are treated by either radiation therapy or surgery, the decision resting primarily on minimizing adverse effects of therapy. The majority of these cancers involve the floor of the mouth and the anterior two-thirds of the tongue. T2 lesions of the floor of the mouth that are deeply invasive carry a 30-40% rate of bilateral neck lymph node involvement and, thus, are treated with external and interstitial radiation that involves both sides of the neck (Holland, Cancer Medicine, 3rd edition, 1993). Care is taken to adequately assess the contralateral neck as many of these lesions approach and cross the midline.

Cancers of the base of the tongue are typically advanced at presentation and thus have a poor outcome. It has been estimated that 75% of these cancers present as Stage III or IV (Pazdur, Medical Oncology, a Comprehensive Review, 2nd edition, 1995). The 5-year survival rate for Stage I disease is 60% and declines steadily by stage to a 5-year survival rate of only 15% in Stage IV disease (Devita, Principles of Oncology, 5th edition, 1997). However, T1 and T2 lesions are quite amenable to therapy with similar outcomes being achieved with surgery or radiotherapy.

Surgery or radiotherapy is also used in the treatment of cancer of the oropharynx (tonsillar fossa, pharyngeal wall, or base of the tongue). However, surgery poses more risk, including regional lymphatic dissemination and increased morbidity. Combination chemotherapy and radiotherapy is used for advanced stage oropharyngeal carcinoma.

Either surgery or radiotherapy may be used to treat tonsillar carcinomas, but the latter is preferred for larger lesions to minimize disfigurement and loss of function that may result from surgery. Radiotherapy has resulted in local control rates of 80-90% for T1 and T2 tonsillar carcinomas and offers the added advantage of treating regional lymph nodes. Multimodality therapy involving surgery followed by radiotherapy is generally employed in more advanced diseased.

It is essential to identify the mechanism by which primary oral tumors metastasize to the mandible in order to spare its structure and function. Depending on whether the tumor invaded the mandible through the gingiva, the dental socket, or the dental pores in the edentulous mandible, determines the need for marginal resection of a part of the mandible (mandibulectomy) or resection of a large primary tumor located posteriorly without involvement of the mandible. Microvascular composite-free grafts from the fibula or iliac crest are currently the most popular and successful choice for mandible reconstruction (CA-A cancer journal for clinicians, Nov/Dec 1995; 45(6):359).

Nasopharynx and Hypopharynx

Anatomically, the hypopharynx is the part of the pharynx that lies just beyond the area that can be visualized by routine examination with a tongue blade and flashlight; 70% of tumors of the hypopharynx occur in the pyriform sinuses (Surg Clin North Am 1977; 57:7). Because these cancers produce few if any symptoms early on in their course, they are usually detected in advanced stages when overall prognosis is quite poor (Devita, Principles of Oncology, 5th edition, 1997). Currently, the accepted treatment for nasopharyngeal cancer is radiotherapy. Combination chemotherapy and hyperfractionated radiotherapy, currently under investigation, has demonstrated increased local control of primary tumors. Also, surgery and brachytherapy is employed in recurrent nasopharyngeal tumors.

Second Primary Tumors

Patients with head and neck cancer are particularly susceptible to the development of a second primary tumor. A study which collected data from 21,371 patients diagnosed with oral or pharyngeal cancer from 1973 to 1987, concluded that the rate of development of second tumors was 3.7% per year. Increased risks persisted unabated for cancers diagnosed 5 or more years after oral cancer, suggesting that the second cancers were new primary tumors and not misdiagnosed metastases. The increased risks of second primary tumors were not race or gender dependent, but were most prominent in patients under age 60. The high rate of second primary tumors points to the great need for medical surveillance and elimination of risk factors (Day GL and Blot WJ, Cancer 1992; 70:14-9).

MULTIMODALITY THERAPY

A multidisciplinary team of health professionals is necessary for the effective management of HNSCC, including a head and neck surgeon, radiation oncologist, medical oncologist, dentist, and counselor. Surgery, radiotherapy and chemotherapy are often combined for maximum benefit. Implementation of multimodal therapy has increased five-year survival in early-stage tongue cancer from 75% to 82%, and Stage III HNSCC, from 37% to 49% (CA-A cancer journal for clinicians, Nov/Dec 1995; 45(6):366).

Early-stage disease (T1 and T2) may be treated with either surgery or radiotherapy; multimodality therapy is usually prescribed in more advanced disease (T3 and T4). Most surgical candidates with advanced stage disease require adjuvant radiotherapy. Postoperative radiotherapy is preferred over preoperative radiotherapy because there are no dose limitations, pathologic staging of the tumor is more accurate and risk of poorly healing wounds is eliminated. Adjuvant radiotherapy is used to help pre-

vent contralateral neck metastasis which occur in approximately 30% of patients with ipsilateral involvement of cervical lymph nodes. Studies have shown improved five-year survival in the one-third of patients who fail initial therapy and develop distant metastasis and another third who develop a second or multiple primary tumors (Vikram B, etal, American Journal of Surgery 1980; 140:580-584).

Lack of accurate criteria to predict response to radiotherapy for individual patients with HNSCC remains a major problem. As new radiotherapy regimens are introduced, the need for predictive assays to ensure suitable individualized patient treatment has intensified. Prediction of the outcome of radiotherapy would facilitate early choice of adequate treatment. Variations in intrinsic radiation sensitivity of cancer cells cannot alone explain differences in therapy outcome and, thus, additional predictive variables have to be defined. In general, Stage I and Stage II cancers respond equally well to radiation or surgery. The chosen treatment is usually that which is the least debilitating. Stage I and II tumors of the base of the tongue respond better to surgery plus radiation therapy or external radiation therapy plus implantation (brachytherapy) than external radiation therapy alone (Housset M, etal, International Journal of Radiation Oncology, Biology, Physics 1987; 13(4):511-516). Stage III and operable Stage IV cancers usually are managed with radiation therapy post-operatively.

Simultaneous or alternating chemotherapy and radiotherapy was demonstrated to be most promising in treating HNSCC. In a three-year follow-up of a randomized trial comparing an alternating radiotherapy and chemotherapy regimen with radiotherapy alone for treatment of HNSCC, the combined approach exhibited superior efficacy. In a two-year follow-up trial, 157 patients were randomized to one of four treatments and assessed for overall survival, progression-free survival, and locoregional relapse-free survival. Patients were assigned to either chemotherapy consisting of four courses of cisplatin (20 mg/m^2) and 5-fluorouracil (200 mg/m^2) for 5 consecutive days during weeks 1, 4, 7, and 10, plus radiotherapy consisting of three courses of 20 Gy, (2 Gy per day during weeks 2-3, 5-6, and 8-9) or 70 Gy of radiotherapy alone (2 Gy per day, 5 days per week). Combined therapy was administered to 80 patients and radiotherapy alone to 77 patients. Disappearance of clinically detectable disease for at least four weeks was observed in 43% of combined-treatment patients and 22% of the radiotherapy-only patients. Five-year estimates of overall survival were 24% in the combined-treatment group compared to 10% in the radiotherapy-only group; five-year estimates of progression-free survival were 21% and 9%, respectively and five-year estimates of locoregional relapse-free survival were 64% and 32%, respectively. Thus, the superiority of alternating chemotherapy and radiotherapy over radiotherapy alone in treating HNSCC was demonstrated at three years and reconfirmed at five years (Merlano M, etal, JNCI, May 1996; 88(9):583-589).

Indications for chemotherapy in HNSCC include treatment of recurrent or metastatic disease, neoadjuvant therapy, adjuvant therapy, and radiosensitization. In addition to the new combined modalities such as sequential and synchronous chemoradiotherapy, advances in organ preservation and chemoprevention that attempts to reverse premalignant lesions and prevent second primary tumors, are promising approaches to extending survival in patients with head and neck cancer. Exhibit 6 estimates the number of HNSCC patients who annually become candidates for chemotherapy treatment (in addition to other modalities) in the USA, Europe and Japan.

Chemotherapy in HNSCC was traditionally limited to patients with locally recurrent or metastatic disease. In this setting, many single agents, including methotrexate, cisplatin, and 5-FU, were used with response rates approximating 10-30%. Regimens that combined agents resulted in higher response rates but not increased overall survival (Murphy BA, etal, Current Opinion in Oncol 1996; 8:221-6).

Currently, standard palliative chemotherapy in progressive disease in patients with a good performance status is a combination of cisplatin (100 mg/m^2) and 5-FU (1000 mg/m^2). A randomized trial of 249 patients showed a 32% response rate when both agents were combined versus approximately half that for either agent used alone. Despite this, survival was similar in all three groups. Toxicity was not significantly greater in the combination chemotherapy group (JCO 1992;10:257). Future studies in this area will focus on endpoints other than simply survival or response rates, including quality of life issues such as pain and symptom control.

The role of neoadjuvant chemotherapy continues to be defined. The theoretical aims of this approach to therapy include decreasing the morbidity of local control measures and decreasing local recurrence and metastatic disease rates with a resulting improvement in survival. The available data suggest that neoadjuvant therapy is indicated for N0 or N1 laryngeal cancer; patients with more extensive disease fared poorly.

The goal of adjuvant therapy is to decrease local recurrence rates in patients treated with definitive local measures with surgery with or without radiotherapy. In addition, another goal is to decrease rates of distant spread and improve survival. An NCI review of a subset of patients with limited oral cavity cancer, found that maintenance chemotherapy resulted in an improved three-year disease-free survival (67% versus 49%) (JCO 1990; 8:838). In another study, 442 patients with oral cavity, oropharynx, hypopharynx, and laryngeal malignancies that were locally advanced but operable, were randomized to either post-resection radiotherapy or chemotherapy and radiotherapy. Those at high risk were treated with higher doses of radiotherapy. There was no significant differences in survival, disease-free survival, or local recurrence rates, but distant metastatic disease rates were lower in the combined treatment group. At this time,

adjuvant chemotherapy is not considered standard of care but further trials are addressing its benefits in high risk patients.

Finally, chemotherapy may be administered in combination with radiotherapy in an effort to decrease local recurrence rates. The theoretical basis for this is that chemotherapy might sensitize malignant cells to the deleterious effects of radiotherapy. A clinical trial treating patients with cisplatin and infusional 5-FU every other week, with split course radiation, reported a 98% response rate and a median survival of just over 3 years (JCO 1989;7:846). Although other trials using other combinations have had promising results, there has never been a large randomized trial to adequately assess this issue. Likewise, the optimal timing of simultaneous versus sequential chemoradiotherapy has not been established.

ANTI-CANCER DRUG DEVELOPMENT

TAXANES — PART II INDICATIONS, MARKETS, FORMULATIONS, ANALOGS AND DERIVATIVES, AND NOVEL SPINDLE POISONS

Introduction of the taxanes paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Rhône-Poulenc Rorer) in the global marketplace has dramatically and irrevocably changed the role and opportunity of drug therapy for the management of cancer. Previously, few drug therapies were considered desirable, with surgery being the primary treatment with curative intent and radiotherapy an adjunct or replacement option in inoperable or more advanced disease. Most drugs on the market had been marketed for several decades, their patents had expired, they were inexpensive, very toxic and offered meager benefits. Even newer drugs were only approved for very narrow indications, their relatively high prices made less significant by their limited potential markets. Taxol changed all that. Although a difficult drug to produce and deliver and associated with severe toxicities, it was introduced at a time when oncologists possessed a variety of tools to deliver complex chemotherapeutic regimens and manage toxic effects. When the National Cancer Institute (NCI) concluded licensing negotiations with Bristol-Myers Squibb (BMS), before Taxol was introduced in the market for the narrow indication as second-line therapy for refractory advanced ovarian cancer, no one anticipated that the potential annual end-user caseload for this drug may exceed one million (see Exhibit 7).

Despite the frenzy surrounding Taxol, the drug itself offers modest benefits. This is not a panacea and it certainly does not cure cancer. The Taxol phenomenon illustrates the incredible demand of the cancer market for anything that offers even the slightest benefit and the willingness to pay for a drug that is at least three times more expensive than most others but definitely not thrice as effective.

CLINICAL STATUS

Ovarian Cancer

Ovarian cancer was the first target for taxanes and the leading indication for Bristol-Myers Squibb's Taxol which has been launched globally as second-line therapy (see FO, p 615) and it is currently considered the standard of care as first-line therapy in combination with cisplatin. The last major market to approve Taxol for the ovarian cancer indication was Japan. Japan's Ministry of Health and Welfare approved Taxol for treatment of ovarian cancer in July 1997, fully 38 months after the application was filed by BMS. The drug was launched in October, 1997 but it is not reimbursed by the National Health Insurance (NHI) system because of pricing disagreements.

Although ovarian cancer has been a low-priority area for Rhône-Poulenc Rorer, competition in this area is expected from Taxotere that demonstrated excellent activity in advanced disease. Ivax' (Miami, FL) version of paclitaxel, Paxene has also been clinically evaluated for this indication. Another taxane, Biolyse Pharma's paclitaxel (see below) is in phase II clinical trials in refractory ovarian cancer.

Breast Cancer

Breast cancer is the leading and fastest growing indication for both Taxotere and Taxol in which they are competing directly for the same patients. However, Taxotere may be slightly ahead of Taxol for this indication because it was approved in Japan in October 1996, where it is marketed by Chugai and where it is reimbursable at the highest allowable premium. The approved regimen in Japan is 60 mg/m^2 infused over one hour, every three weeks. Ivax and Biolyse have also carried out clinical trials with their versions of paclitaxel for this indication.

Kaposi's Sarcoma

Kaposi's sarcoma (KS) has become the third major indication for single-agent paclitaxel therapy, following ovarian and breast cancer. Taxol's sNDA (#20-262/S-022) filed in February 1997, was approved by the FDA in August 1997. At the same time Taxol was designated as an orphan drug and, therefore, gained a 7-year market exclusivity.

On June 23, 1997 the FDA's Oncology Drugs Advisory Committee (ODAC) unanimously recommended approval of Taxol for the treatment of KS. ODAC based its decision on results from two phase II trials involving 85 KS patients, one conducted at NCI, involving 29 patients, and the other at the University of Southern California in Los Angeles and Harvard Medical School (Boston, MA), involving 56 patients. Response rates were 59% and 69%, respectively. Mean duration of response was 8.2 months. Two dosage levels, to be infused over three hours, were recommended, 135 mg/m^2, every three weeks or 100 mg/m^2, every two weeks. Of the 85 patients enrolled in the two studies, 59 had been treated with prior systemic

Exhibit 7
Worldwide Candidate Populations for Taxane-based Chemotherapy

Cancer Site	Approved and Pending Indications WW	Estimated Affected Populations WW per Year	Additional Indications under Investigation and Off-Label Indications	Estimated Affected Populations WW per Year	Total WW Potential Treatment Population per Year
Breast Cancer	2nd line therapy for metastatic disease *(docetaxel, paclitaxel, WW)*	38,407	1st line therapy for early-stage and advanced stage disease	363,319	401,726
Non-Small Cell Lung Cancer	2nd line therapy *(docetaxel, outside the USA)*	106,860	1st line therapy in advanced disease	174,742	261,602
Ovarian Cancer	1st line therapy *(paclitaxel + cisplatin or carboplatin in the UK*)* 2nd line therapy in refractory disease *(paclitaxel)*	100,661			100,661
Cervical Cancer			Locally advanced disease	42,665	42,665
Head and Neck Cancer			Metastatic or recurrent advanced disease	33,201	33,201
Karposi's Sarcoma	2nd line therapy for refractory AIDS-related KS *(paclitaxel, approved in the USA)*	11,000	Advanced disease	103,766	11,000
Other Solid Tumors				717,693	103,766
Total		256,928			954,621

** Currently standard therapy on an off-label basis in many countries*

therapy, and 38 with anthracycline-based therapy. High efficacy was reported in patents who were previously treated with anthracycline-based chemotherapy, or who were resistant or intolerant to prior chemotherapy. Concerns raised regarding these trials included small sample size, lack of comparative arms, inadequate controls in follow-up, and lack of pharmacokinetic and drug interaction data. Eight ODAC members voted to recommend full approval of the drug while the other four recommended accelerated approval, which requires a phase IV trial while the drug is being marketed. The FDA opted for the full approval option.

The drug's safety profile paralleled that experienced with previously treated ovarian and breast cancer. The most common side effect was myelosuppression. It was reported that 17% of patients died within 30 days of initiation of the Taxol regimen but the deaths could not be specifically linked to therapy. Although the 100 mg/m^2 regimen caused fewer hematologic and non-hematologic malignancies, ODAC did not reach a conclusion as to which regimen to recommend. However, the FDA raised concerns over the toxicity of the 135 mg/m^2 dosage level which has been advocated by BMS because of its large dossier of safety data with this dose. Currently, a randomized phase III clinical trial is being conducted by the Eastern Cooperative Oncology Group to study the effects of Taxol in combination with protease inhibitors for the treatment of KS, as well as a phase III trial of Taxol in combination with Sequus Pharmaceutical's (Menlo Park, CA) Doxil (liposomal doxorubicin).

On September 19, 1997 ODAC also unanimously approved Paxene for the KS indication, based on a clinical trial involving 89 patients with refractory AIDS-related KS. At a dose regimen of 100 mg/m^2, infused over three hours, every two weeks, the overall response rate reported by Ivax' principal investigator, Parkash Gill, MD, of the University of Southern California at San Diego, was 46%, including 2 (2%) CR and 39 (44%) PR. The FDA, however, reported that the respose rate was 42%, all PR. Time to disease progression was 164 days. A expected, the drug was associated with significant toxicities, including a 74% incidence of neutropenia which was a contibuting

factor in the death of three patients from sepsis. The safety profile of the drug may also need to be evaluated in patients being treated with protease inhibitors.

Lung Cancer

Treatment of non-small-cell lung cancer (nsclc) is the next major indication for taxanes. Taxotere has already been approved for this indication in many major markets outside North America, including Japan. BMS plans to file for this indication in the USA and elsewhere in the next few months. Biolyse has also carried out clinical trials in this area.

Combination Regimens

Taxane-based combination regimens may eventually prove to be the treatment of choice in advanced disease for many lower indications. Numerous combinations with established agents are being currently evaluated for a variety of solid tumors with good results.

Paclitaxel is also being investigated in combination with various novel agents in development. A 450-patient phase III clinical trial, as second-line treatment of advanced breast cancer, is ongoing in combination with a humanized MAb targeted against a protein receptor, Her-2/neu on tumor cells, under development by Genentech (South San Francisco, CA). The trial is randomizing patients to the MAb plus cyclophosphamide and doxorubicin or paclitaxel.

TECHNICAL CHALLENGES

Biomass Sources

Although paclitaxel is a difficult drug to produce, formulate and administer, its source is widely available and extracts may be easily obtained. Numerous sources of bulk product have emerged worldwide; some suppliers, particularly from China, are contacting potential clients by e-mail and offering bulk paclitaxel and related compounds. However, in order to develop a viable product that may be approvable for clinical applications in the West, it would be necessary to demonstrate bioequivalence with approved versions of paclitaxel. It is not clear if that would require that the extraction/synthesis process is identical to that used for the production of Taxol which has been patented. Such a scenario would preclude generic versions from entering the market. Paclitaxel versions produced by different methods may be viewed as new drugs and required to enter clinical trials in order to seek approval. Only one other version of paclitaxel, that manufactured by Hauser (Boulder, CO), that was the first FDA-approved version of Taxol, may be exempt from proving bioequivalence.

Any submission for FDA approval of a paclitaxel version must be accompanied by an environmental impact statement, required by the Environmental Production Agency (EPA), that specifies the source of the drug. It is implied that ANDAs should specify sources other that naturally-occurring Pacific yew trees in order to be considered for approval. However, overseas sources and taxus plantations appear capable to produce sufficient biomass to satisfy the market.

Formulations

One of the major drawbacks of currently commercialized taxanes is that they are insoluble in water. This property makes administration difficult, requiring lengthy slow infusion. Cremophor El which is the standard solubilizer used with Taxol, may also cause problems in some patients. Several companies are using different solubilizers to reduce complications.

Administration Routes

Currently, most clinical trials have used intravenous forms of paclitaxel and docetaxel. Naturally, an oral form would be a major breakthrough in this area. However, bioavailability appears to be a limiting factor. An oral form of paclitaxel is being tried in a phase I clinical trial in combination with cyclosporin which appears to enhance bioavailability.

MARKET OPPORTUNITY

Taxol has become the most successful oncology drug ever and is considered the growth engine for BMS in the short-term. Available in 76 countries, it is expected to generate sales of approximately $1 billion in 1997. Also, as Taxol effectiveness, alone or in combination, is demonstrated for more and more indications, future demand for the drug appears impressive (see Exhibit 7). In late 1997, BMS reported that its R&D investment in Taxol has exceeded $500 million. The company has sponsored more than 500 clinical trials representing a combined enrollment of over 40,000 patients. There is no doubt that BMS will dominate this market in 1998, irrespective of any competitors. Ivax' Paxene, if approved, may be the only competitor in the USA but, in order for Paxene to have an impact, it would need to be used extensively off-label because its approved indication, Kaposi's sarcoma, represents a very small market. Parenthetically, an identical version of paclitaxel as Paxene, also produced by NaPro BioTherapeutics, has been marketed by F. H. Faulding as Anzatax in Australia since 1995.

Also, it appears that BMS may be losing its battle to keep generic paclitaxel from the European market where competitors are attempting to declare "use" patents invalid. So far, this argument has worked in the Netherlands where the judge refused to grant BMS an injunction against Yew Tree Pharmaceuticals (Haarlem, the Netherlands) to prevent it from marketing its version of paclitaxel. It is unlikely that this will be the case in the USA market in the short term. Observers believe that it will take at least a couple of years for this issue to be resolved in the USA. However, even if BMS is able to fend off generic competition for a few years, it will undoubtedly have to share some of its market with Taxotere which is proving even more effective when compared head on with Taxol in selected indications (see Exhibit 8).

Naturally, one of the main reasons for the market success of taxanes are their high costs. List price of one milligram of Taxotere range from $10 to $15, depending on the country where it is being marketed. Taxol milligram prices are lower, estimated at $6 to $10, but because its recommended treatment regimen requires higher doses, variations become less relevant when comparing overall treatment costs per case which range from $5,000 to $15,300. Average treatment costs in the USA are estimated at $8,000. Clearly, based on the potential demand of these drugs, a generic version, priced at 25% of prevailing charges, could potentially save the global healthcare systems billions of dollars.

PACLITAXEL EXTRACTS AND SEMI-SYNTHETIC VERSIONS

Aphios

Aphios (Woburn, MA) produces paclitaxel using needles of the ornamental yew tree by a proprietary patented process (SuperFluids) and also formulates it in liposomes. Currently, Aphios produces pilot quantities of paclitaxel and sells it to researchers.

Biolyse Pharma

Biolyse Pharma (Port Daniel, Quebec, Canada) developed technology to extract paclitaxel from the twigs and needles of the yew species *Taxus canadensis* commonly found in the provinces of Ontario, Quebec and northern New Brunswick. The Canadian Health Protection Branch (HPB) has authorized Biolyse to conduct trials in refractory metastatic breast, non small cell lung and ovarian cancer. Phase II clinical trials have been in progress over the last three years at the Hotel Dieu de Montreal Hospital (affiliated with the University of Montreal), the Jewish General Hospital in Montreal (affiliated with McGill University and numerous other regional hospitals in Quebec) as well as the London Ontario Regional Cancer Center.

BioNumerik Pharmaceuticals

BioNumerik Pharmaceuticals (San Antonio, TX) has developed a non-cremophor-based formulation of paclitaxel.

Bio-Technology General

In July 1994, Bio-Technology General (BTG; Iselin, NJ) entered into a 17-year agreement with Shenzhen Boda Natural Product Company (Shenzhen, People's Republic of China) for exclusive marketing rights to a generic version of paclitaxel (see FO, p 182). Recently, the company said that this was a low priority endeavor.

Cytoclonal Pharmaceutics

Cytoclonal Pharmaceutics (Dallas, TX), holds an exclusive worldwide license from the Research and Development Institute at Montana State University (Bozeman, MT) and the Montana College of Mineral Science and Technology, to use patented technology (issued in 1994) to synthesize paclitaxel from yew biomass using a combination of extraction and microbial fermentation techniques. A paclitaxel-producing fungus, *Taxomyces andreanae*, originally isolated from the Pacific yew tree, has been adapted to grow independently by using fermentation processes. This fungus produces paclitaxel and other taxanes such as docetaxel, that are equivalent to those produced by other processes. In July 1996, Cytoclonal licensed rights to a yew tree gene from Washington State University Research Foundation (Pullman, WA) to use in the biosynthesis of paclitaxel.

ChiRex

ChiRex (formerly SepraChem; Stanford, CT) is a contract manufacturing organization specializing in the development and supply of fine chemicals and chiral intermediates. ChiRex possesses a proprietary process technology for production of semi-synthetic paclitaxel that it intends to supply to pharmaceutical companies.

Gensia Sicor

Gensia Sicor (San Diego, CA), a supplier of multisource injectable oncology drugs, expects to file an ANDA at the end of 1997 for its generic version of paclitaxel.

Phytogen Life Sciences

Phytogen Life Sciences (formerly Towers Phytochemicals and TPL Phytogen; Vancouver, BC, Canada) has focused substantially all of its resources to date on the development of a manufacturing process and the construction of a facility for the production of commercial quantities of paclitaxel. Phytogen has negotiated agreements with British Columbia's major forest products companies for Pacific yew bark harvesting rights, that may provide a continuing source of supply for several years. Through these agreements, Phytogen has effective control of most of BC's supply of Pacific yew materials. In order to diversify and expand its sources, Phytogen has also entered into an exclusive contract with a major supplier outside North America. Also, the company has completed a major research project for rapid mass propagation of yew trees, and, for the mid-term, has plans to derive raw material from plantation sources. In 1994 the company completed construction of a 22,000 square-foot building in Delta, BC, which is equipped to produce paclitaxel as a bulk pharmaceutical product to clinical purity standards under cGMP. In 1996 Phytogen filed a Drug Master File with the FDA in preparation for marketing its paclitaxel in the USA. In September 1996, Phytogen International, a subsidiary of Phytogen Life Sciences, awarded Mylan Pharmaceuticals (Pittsburgh, PA) an exclusive license to market generic paclitaxel in North America. Under the agreement, Mylan will purchase bulk product from Phytogen and will manufacture the drug using licensed technology. In early 1997, Draxis Health (Toronto, Canada) acquired rights for paclitaxel in Canada from Mylan. In August 1995, Drug Royalty (Toronto, Ontario, Canada) acquired for Can$1.5 million

($1 million), an interest in Phytogen's paclitaxel revenue consisting of license fees and direct sales and royalties. In August 1997, Drug Royalty invested an additional Can$3 million ($2.1 million) in Phytogen in exchange for increased royalty. NeXstar Pharmaceuticals (Boulder, CO) holds an equity position in Phytogen.

Samyang Genex

Samyang Genex (formerly Sun Hill Glucose; Seoul, South Korea), a subsidiary of the South Korean company Samyang, aquired, in September 1995, all interest in paclitaxel and other taxoids from ESCAgenetics and its subsidiary, PHYTOpharmaceuticals (see FO pp 182-183) that subsequently liquidated their biotechnology facility in San Carlos, CA, in June 1996.

Wex

Wex (Vancouver, BC, Canada) plans to produce and sell raw paclitaxel to pharmaceutical companies. Wex has completed the construction of a manufacturing operation, Nanning Maple Leaf Pharmaceutical (Nanning, Guangxi, People's Republic of China), as part of a 51%-49% joint-venture with the Chinese company, Pharos Pharmaceutical.

NOVEL DRUG DELIVERY SYSTEMS

Currently marketed taxanes, while appearing very effective, can also have significant adverse side effects when systemically administered. A number of groups are formulating paclitaxel in various vehicles to mitigate its shortcomings and, in the process, create a new product to circumvent BMS' exclusivity.

Guilford Pharmaceuticals

Guilford Pharmaceuticals (Baltimore, MD) announced in June 1997, that it was issued a USA composition of matter and use patent, # 5,626,862, entitled "Controlled Local Delivery of Chemotherapeutic Agents for Treating Solid Tumors" that relates to the delivery of a range of cancer chemotherapeutic agents in biodegradable polymers for the targeted and controlled treatment of solid tumors. This patent contains claims relating to various polymers in conjunction with certain types of chemotherapeutic agents, including paclitaxel, as well as the topoisomerase I inhibitor, camptothecin, and local delivery of such anti-cancer compounds for the treatment of solid tumors. Guilford has exclusively licensed rights to this patent from Massachusetts Institute of Technology (Cambridge, MA) and Johns Hopkins University (Baltimore, MD).

Matrix Pharmaceuticals

Matrix Pharmaceuticals (Fremont, CA) has developed a series of Anhydrous Delivery Vehicles (ADVs) that in preclinical experiments significantly enhance local efficacy of drugs compared to systemic delivery. These ADVs may be applicable to various water-insoluble drugs and Matrix has designed an ADV formulation of paclitaxel. The technology may also lend itself to water-soluble drugs that exhibit limited stability when dissolved in aqueous media. A patent for the ADV technology was granted in 1996 in the USA, and similar patent claims have been filed in Europe and Japan.

NeoPharm

NeoPharm (Lake Forest, IL) has obtained rights to liposome-encapsulated Taxol (LET) from Georgetown University (Washington, DC); LET has the potential to decrease the toxicity of the drug and, thereby, permit a much shorter, outpatient course of therapy which could potentially greatly decrease treatment costs. In addition, LET may potentially overcome the problem of multi-drug resistance (MDR). The liposome formulation in LET is based on cardiolipin, a lipid found in cardiac tissue; NeoPharm has developed a synthetically derived cardiolipin, which may provide a reliable lipid source for making liposomes to be used in upcoming clinical trials.

Phytogen Life Sciences

Phytogen Life Sciences has concluded an exclusive worldwide license agreement for an advanced formulation of paclitaxel developed by a university in the USA. This patented technology was particularly promising in early small animal tests that indicated that the delayed, mechanism-based toxicity of the drug itself was reduced despite a higher maximum tolerated dose, resulting in equal or better anti-tumor potency. More significantly, other taxanes, in addition to paclitaxel, can be formulated using this technology, including docetaxel and other analogs.

Sparta Pharmaceuticals

Sparta Pharmaceuticals (Horsham, PA) has licensed from Research Triangle Pharmaceuticals (RTP; Durham, NC), a drug delivery technology (Spartaject) that accommodates poorly water-soluble and water-insoluble compounds by encapsulating them with a fatty (phospholipid) layer. In this approach, submicron or near micron size drug particles are coated with a membrane-forming phospholipid layer creating a suspension rather than a solution so that the drug can be delivered intravenously without use of potentially toxic solubilizing agents. Therefore, Spartaject may reduce toxicity and, potentially, increase efficacy of compounds that cannot be delivered intravenously because of solubility-related formulation problems. RTP and Sparta may pursue a joint venture to evaluate and develop paclitaxel and related derivatives using the Spartaject technology. If the terms of the joint venture are not agreed upon by the end of 1997, RTP may license rights to this technology to another party.

SuperGen

SuperGen (San Ramon, CA) announced, in October 1996, that it received a USA patent allowance for its proprietary Extra technology for use in the reformulation of anti-cancer drugs which is being applied to paclitaxel, among other agents. The Extra technology is designed to

Exhibit 8
Response Rates Associated with Taxane Therapy

Clinical Setting	Response Rate (CR+PR) (%)	
	Paclitaxel	Docetaxel
Metastatic breast cancer		
First-line single-agent chemotherapy	29-63 (175-250 mg/m^2)	43-69 (75-100 mg/m^2)
First-line combination chemotherapy (various agents)	28 (135 mg/m^2) 28-45 (225 mg/m^2) 43 (250 mg/m^2)	23-74 (75-100 mg/m^2)
Second-line single-agent chemotherapy in anthracycline-resistant disease	18-26 (175 mg/m^2) 6-55 (250 mg/m^2)	28-50 (100 mg/m^2)
Second-line combination chemotherapy (various agents) in anthracycline-resistant disease	84 (100-125 mg/m^2)	15-29 (100 mg/m^2)
First-line single-agent neoadjuvant chemotherapy (Gradishar WJ, Oncology, August 1997, Supp 8:15-18)		85 (100 mg/m^2)
Second-line single-agent chemotherapy in alkylating agent-resistant disease (Chan S, Oncology, August 1997, Supp 8:19-24)	33 (135-200 mg/m^2)	47 (100 mg/m^2)
Non-small-cell lung cancer (nsclc)		
First-line combination chemotherapy (various agents)	25 (135-200 mg/m^2) 16 (135-400 mg/m^2) 32 (210 mg/m^2)	29-70 (60-100 mg/m^2)
Advanced head and neck cancer		
First-line single-agent chemotherapy	38 (escalating doses 40-90 mg/m^2/week)	31-50 (100 mg/m^2)
Advanced gastric cancer		
Second-line single-agent chemotherapy in refractory disease	0 (escalating doses 40-90 mg/m^2/week)	14-26 (100 mg/m^2)
Advanced ovarian cancer		
First-line single-agent chemotherapy	21 (40-100 mg/m^2) 29 (135-175 mg/m^2) 41 (175-230 mg/m^2)	30 (100 mg/m^2)
First-line combination chemotherapy with platinum-based agents	50 (135-175 mg/m^2)	58 (75-85 mg/m^2)
Second-line single-agent chemotherapy in platinum-resistant disease	20-50 (135-175 mg/m^2)	20-31 (100 mg/m^2)

Source: Various published results from clinical trials reported elsewhere in FUTURE ONCOLOGY.

enhance the safety profile and handling characteristics of certain existing anti-cancer drugs by providing stable, ready-to-inject solutions that lessen handling risks for health care providers associated with mixing current powder formulations prior to injection, and diminish ulceration risks to patients by "shielding" the drug at the injection site. In May 1997, SuperGen signed a letter of intent with a Chinese supplier to secure an ongoing source of paclitaxel, which it intends to commercialize under the brand name Paclitaxel Extra if it succeeds in gaining FDA approval.

Xechem International

Xechem International (New Brunswick, NJ), a biopharmaceutical company deriving drugs from natural sources, entered, in September 1997, into a licensing agreement with the University of Texas M. D. Anderson Cancer Center (Houston, TX) for a new formulation of paclitaxel that does not incorporate such solubilizing agents as cremophor or ethanol. Xechem recently received a broad process patent for the extraction, isolation and purification of paclitaxel from any Taxus species containing raw biomass. The company is obtaining raw biomass from a Chinese source.

NEXT GENERATION OF TUBULIN STABILIZING DRUGS/SPINDLE POISONS

Epothilones

Epothilones are novel compounds extracted in 1996 from the bacterial strain, *Sorangium cellosum*. Unlike the complex nature of the paclitaxel molecule, epothilones have a simpler structure but act by a similar mechanism to induce tubulin polymerization and microtubule stabiliza-

tion. K. C. Nicolaou, PhD, and his team at Scripps Research Institute (La Jolla, CA) has synthesized numerous analogs of epothilones using combinatorial chemistry techniques. Two members of this group, epothilones A and B, were selected and, of these, epothilone B appeared to be more potent than paclitaxel and was also active against paclitaxel-resistant cells *in vitro*. Also, among synthesized compounds, four or five were even more potent than epothilone B. This work was performed in collaboration with Novartis. It is also reported that several other drug companies are working with these compounds. In July 1997, Bristol-Myers Squibb entered into a three-year agreement with Gesellschaft für Biotechnologische Forschung (GBF; Braunschweig, Germany) to develop epothilones for the treatment of cancer.

Eleutherobin

Eleutherobin, an extract from a coral found in the waters of India and Australia, was also shown to be a spindle poison. The compound, isolated in 1997 by Bill Fenical, PhD, at Scripps Institution of Oceanography (La Jolla, CA), under a program funded by the NCI, has been synthesized and licensed to Bristol-Myers Squibb. This discovery could not have come at a more appropriate time as it appears that only a few milligrams of the natural extract remain because the coral is no longer being harvested. Eleutherobin has a different structure than paclitaxel but acts by the exact same mechanism.

RPR-109881

Rhône-Poulenc Rorer is developing a new taxane analog, RPR-109881, as both an oral and IV formulation. The drug crosses the blood-brain barrier and is active against MDR tumors, including those resistant to paclitaxel. It is in phase I clinical trials.

MEETING COVERAGE

NEW APPROACHES FOR THE TREATMENT OF HEAD AND NECK CANCER

FROM THE 33RD ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY DENVER, CO, MAY 17-20, 1997

MULTIMODALITY THERAPY

Taxanes

Docetaxel (Taxotere; Rhône-Poulenc Rorer) showed promising activity when combined with standard therapy in treating HNSCC. In a phase I/II trial, 23 patients with locally advanced previously untreated HNSCC, were treated with daily docetaxel (60 mg/m^2), in conjunction with a modified version of a standard treatment with daily cisplatin (25 mg/m^2), 5-FU (700 mg/m^2), and a continuous IV infusion of leucovorin (500 mg/m^2), along with granulocyte-colony stimulating factor (G-CSF). Patients were treated with three cycles, at four week intervals, before twice daily radiotherapy. Planned surgery for a partial response in the neck was performed after radiotherapy.

At a 12-month median follow-up, objective overall response rate was 100%, with 61% (14/23) CR and 39% (9/23) PR. Pathologic CR rate at the primary site was higher than expected with standard cisplatin, 5-FU and leucovorin treatment, as well as other combination therapies. Docetaxel obviously substantially enhances treatment efficacy. Clinically significant side effects reported include febrile neutropenia, renal tubular concentrating defect and mucositis. However, although adverse events are formidable, results justify further trials in selected patient populations if responses remain high (Posner M, etal, ASCO97, Abs 1380:387a).

Paclitaxel (Taxol; Bristol Myers Squibb), administered pre-operatively in combination with carboplatin (Paraplatin; Bristol Myers Squibb) and radiation, is associated with a high rate of pathologic CR at the primary site and a high level of organ preservation in patients with advanced HNSCC. Because numerous pre-operative chemotherapy or chemoradiation protocols have shown high clinical response rates but only modest complete pathologic responses for large primary tumors, a phase II study was initiated in which 34 patients with advanced HNSCC were treated with weekly paclitaxel (60 mg/m^2) and carboplatin (AVC of 1) plus concurrent fractionated external beam radiation (45 Gy). This regimen was followed by organ preservation surgery when applicable, to maximize local regional tumor control. Patients with positive biopsy underwent definitive surgery in four to five weeks, while those with a negative biopsy were treated with an additional three weeks of radiation for a total dose of 72 Gy. Of 26 evaluable patients, 19 (73%) experienced CR and six PR (23%), for a total clinical response rate of 96%. A pathologic CR at the primary tumor site occurred in 17 (71%) of 24 patients (two had unknown primaries). At median follow-up of nine months, progression-free survival was 70% and overall survival was 87% (Wanabo HJ, etal, ASCO97, Abs. 1397:391a).

Thymidylate Synthase Inhibitors

AG337 (Thymitaq: Agouron Pharmaceuticals), a novel thymidylate synthase inhibitor (see FO, p 55), has demonstrated good clinical activity, while being well tolerated, in patients with pretreated HNSCC. In a multicenter phase II clinical study, 22 patients with histologically confirmed HNSCC (21 had undergone prior surgery, 25 had been treated with prior radiotherapy, and 13 had been treated with chemotherapy), were treated with Thymitaq (1000 mg/m^2) as salt weight, administered daily as a continuous infusion over five days. In each patient, the dose could be modified based on the toxicities observed during the first treatment course (every three weeks). In this group, overall response rate was 22% (6/27)

with 2 CR and 4 PR. Duration of response in patients with CR was 16+ (still ongoing) and 20 months, while in those with PR, it ranged from three to six months. Overall, the drug was well tolerated and its most common toxicities, i.e., stomatitis and rash, were reduced with premedication (Belani CP, etal, ASCO97, Abs. 1381:387a).

RADIOSENSITIZATION

Tirapazamine

Tirapazamine (Tirazone; Sanofi), an agent which shows preferential cytoxicity to hypoxic tumor cells, was found to be well tolerated and effective when used in combination with radiotherapy for the treatment of advanced HNSCC. To assess the efficacy and safety of this combination regimen in advanced HNSCC, 40 patients with previously untreated HNSCC were treated with conventional radiotherapy (70 Gy) for seven weeks, with concurrent IV tirapazamine (159 mg/m^2) thrice weekly for 12 doses. Advanced HNSCC is an ideal setting in which to test the efficacy of tirapazamine because computerized PO_2 measurements found that some regions of head and neck tumors are consistently hypoxic. Planned follow-up was carried out at eight and 26 weeks.

At eight weeks follow-up, there were 16 CR, 11 PR and disease progressed in two; among 11 non-assessable patients, 8 withdrew too early to evaluate. At 26 weeks follow-up, there were 20 CR, 3 PR and disease stabilized in one and progressed in seven; 9 patients were not assessed, including six who withdrew early and two who did not complete the 26-week follow-up. Regarding the safety profile of tirapazamine, acute drug toxicities that included muscle cramps (86%), nausea (17%), and vomiting (27%) were generally ameliorated by supportive care. Three patients experienced drug-related Grade 3 toxicities and six Grade 4 toxicities; only two of these cases involved hematologic toxicity (Trotti A, etal, ASCO97, Abs. 1379:387a).

CHEMOTHERAPY

Vinorelbine

A trial using vinorelbine (Navelbine; Glaxo Wellcome) monotherapy which has shown some level of activity in patients with locally advanced or metastatic HNSCC, was carried out in 40 patients with HNSCC. Treatment consisted of weekly vinorelbine (30 mg/m^2) and lasted until disease progression. In 35 evaluable patients, overall response rate was 14%, with one CR and four PR. Median progression-free interval was two months. Overall, the drug was well tolerated; the major drug-related adverse event was neutropenia, with 25 of the 40 (62.5%) patients having Grade 3 or 4. In addition, 17.5% experienced Grade 3 or 4 anemia and 17.5% documented infections, one fatal (Canfield VA etal, ASCO97, Abs. 1382:387a).

A related presentation reported that combination therapy with vinorelbine, UFT (Bristol-Myers Squibb), and cisplatin is a very active regimen for the treatment of locally advanced HNSCC. Vinorelbine and UFT had previously been shown to be promising as monotherapies in HNSCC and both drugs and cisplatin have no overlapping toxicities. A study, therefore, was designed to evaluate the efficacy and safety of this three-drug combination in patients with HNSCC. Forty-seven patients with locally advanced HNSCC were treated with IV cisplatin (100 mg/m^2) on day one, IV vinorelbine (25 mg/m^2) on days one and eight, and oral UFT (6 mg/m^2) on days one to 21, for four cycles. All patients were evaluable for response and toxicity.

The overall response rate was 93%, with 26 CR (55%) and 18 PR (38%); disease stabilized in three patients (6%). Of 18 CR patients who were biopsied at the primary site, 16 had no residual disease. No patient progressed under chemotherapy. Forty-two patients completed locoregional treatment (radiotherapy with (12) or without (30) surgery) and 40 were disease-free at the time of presentation; the two who progressed were alive with disease. The main toxicity was granulocytopenia, with Grade 3/4 neutropenia reported in 76% of patients; there were 19 cases of febrile neutropenia, and one toxic death caused by neutropenic sepsis. Non-hematological toxicities were mild to moderate (Rivera F, etal, ASCO97, Abs. 1376:386a).

GENE THERAPY

Adp53

Adenovirus-mediated p53 (Adp53) gene therapy, using the tumor suppressor gene p53, under development by Introgen Therapeutics (Austin, TX) in collaboration with RPR Gencell (Santa Clara, CA), was shown to be safe, well-tolerated, and clinically active in patients with head and neck cancer. A phase I dose escalation trial was designed to test the efficacy, toxicity, and safety of escalating doses of p53 gene via an adenovirus vector delivery system with 106 to 1010 plaque forming units (pfu) per dose injected directly into the tumor. There were two treatment groups. The resectable group included 13 patients who were treated with Adp53 injected intratumorally three times weekly for two consecutive weeks, and then underwent resection with Adp53 administered intra-operatively and again 72 hours postoperatively. Another 17 patients with unresectable disease were treated with Adp53 injections every other day for two weeks (six injections) into a single lesion, were observed for two weeks, and then the treatment cycle was repeated until disease progression at any disease site.

The objective response rate in resectable patients was 38%, with five of the 13 responders remaining free of disease (total disappearance of all measurable signs of cancer) for more than six months post-surgery. Three individuals died of their cancer and the other five patients were alive with recurrent disease at the time of presentation. Of the 17 non-resectable cases, seven demonstrated some degree of clinical activity in the treated lesion; by

the end of the trial, two patients experienced PR, disease stabilized in five and progressed in six. Therapy was well tolerated, with no serious adverse events attributable to the treatment (Clayman GL, etal, ASCO97, Abs. 1363:382a).

EPIDERMAL GROWTH FACTOR RECEPTOR ANTAGONIST

C225

C225, an epidermal growth factor (EGFr) antagonist, under development by ImClone Systems (New York, NY), proved to be well tolerated and demonstrated biologic activity and stabilization of disease in combination with cisplatin, in patients with HNSCC or lung cancer. The agent is a chimeric monoclonal antibody that binds EGFr and blocks ligand-induced activation of the receptor, inhibiting growth of human cancer cells expressing EGFr *in vitro* and *in vivo*.

A phase Ib/IIa, multicenter dose escalation study of C225 and cisplatin, to evaluate the safety and pharmacokinetics of C225, began in May 1995 and was completed in November 1996, involving 22 patients with advanced HNSCC and non-small cell lung cancer (nsclc). Patients were treated with four weekly C225 infusions of 5.0, 20, 50, 100, 200, or 400 mg/m^2 administered over 10 to 120 minutes. Cisplatin was administered as a 60 mg/m^2 IV infusion every four weeks. Tumors were evaluated every four weeks and patients without disease progression were treated for up to 12 weeks.

Pharmacologically relevant concentrations of C225 were achieved at dose levels of 100 mg/m^2 and optional saturation was achieved at approximately 200 mg/m^2. Of the nine patients with advanced disease treated at these dose levels, one showed disease progression, six demonstrated stable disease and two achieved PR. Biologic activity of C225 was demonstrated at 200 mg/m^2 and 400 mg/m^2 by two head and neck cancer patients, one with a minor response and one with a PR, respectively. Mild to moderate allergic reactions were observed, but none were dose limiting.

Two other phase Ib/IIa dose escalation trials are being carried out using C225 in combination with other anticancer therapies for the treatment of head and neck cancer. They include an NCI-sponsored trial at the University of Alabama, Birmingham, measuring the effectiveness of C225 in conjunction with radiation therapy and a trial of C225 as a single-agent regimen in combination with surgery at the University of Virginia (Falcey J etal, ASCO97, Abs. 1364:383a).

INTERFERON-A

Induction

Induction with IFN-α-2b (Intron; Schering-Plough) followed by chemotherapy and radiation is a curative and organ-preserving approach for the majority of patients with previously advanced HNSCC. In two consecutive phase II trials, conducted between November 1989 and March 1993, 161 patients with previously untreated advanced HNSCC were treated with neoadjuvant subcutaneous IFN-α-2b (2 MU/m^2) on days zero to five, IV cisplatin (100 mg/m^2) on day one, daily continuous infusion of 5-FU (640 mg/m^2) on days one to five, and either oral leucovorin (100 mg) every four hours on days one to five (n=71) or continuous infusion of the L stereoisomer of leucovorin (300 mg/m^2) on days one to five (n=90). Patients then proceeded to a daily continuous infusion of 5-FU (800 mg/m^2) for five days, oral hydroxyurea (1000 mg) every 12 hours for 11 doses and daily radiation (200 cGy), concurrently, for five days. Cycles were repeated every 14 days until the radiation dose reached a total dose of over 7000 cGy. Surgical resection was an optional component of local therapy and was performed in 62 cases. After neoadjuvant chemotherapy, 63% of patients achieved CR; progression-free survival rate was 65% at five years and overall survival rate to date was 50%. Acute toxicity was a major problem with eight deaths; serious mucositis and myelosuppression affected over 90% of patients. Local tumor recurrence risk, the most common pattern of failure was low at 21%. Distant metastases were infrequent, occurring in only 7% of patients (Kies MS, etal, ASCO97, Abs. 1389:389a).

Biochemoprevention

The administration of interferon-α (IFN-α), in combination with 13-cis retinoic acid, and α-tocopheronal was well tolerated and active in the reversal of advanced premalignant lesions in the upper aerodigestive tract which are usually associated with a high malignant transformation rate and are resistant to retinoid intervention alone. Based on earlier preclinical and clinical studies, a 12-month, phase II, biochemoprevention trial of daily 13-cis retinoic acid (100 ng/m^2), twice weekly IFN-α (3 MU/m^2) and daily α-tocopherol (1200 IU) was designed, at the time of presentation, has enrolled 15 patients, and nine with laryngeal and six with oral premalignant lesions. Ten patients completed six months and eight 12 months. At six months follow-up, the overall response rate was 60%, with five CR (four histologic CR) and one PR. There also were two minor responses, disease stabilized in one and progressed in one. At 12 months follow-up, there were four CR, one minor response, disease stabilized in two and progressed in one. Treatment was well tolerated (Papadimitrakopoulou VA, etal, ASCO97, Abs. 1366:383a).

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NEW MEDICINE, INC. MAILING ADDRESS:

P.O. Box 909
Lake Forest, California 92630
Tel: 714. 830. 0448 ■ Fax: 714. 830. 0887
e-mail: newmedinc@aol.com
www:http://www.wp.com/new_med/

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