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STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

PROSTATE CANCER — PART III CURRENT TREATMENT MODALITIES

SPECIAL MID-YEAR REVIEW

OVERVIEW OF ONCOLOGY TRENDS — PART I

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MEETING COVERAGE

ADVANCES IN THE TREATMENT OF BREAST CANCER

FROM THE 34TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY LOS ANGELES, CA; MAY 16-19, 1998

STATE-OF THE-ART IN THE MANAGEMENT OF CANCER

PROSTATE CANCER — PART III CURRENT TREATMENT MODALITIES

Current treatment approaches for all stages of prostate cancer were discussed in great detail in previous FUTURE ONCOLOGY issues (see FO, pp 292-300 and 302-311). This article highlights certain recent developments.

Prostate cancer treatment is mandated by disease stage. The objective is to cure locally-confined prostate cancer and to palliate metastatic disease for which there is no cure. Because most cases of prostate cancer involve localized disease (Exhibit 1), 5-year survival rates have been traditionally high (Exhibit 2), mostly because of surgical intervention that has, in the past, been the gold standard for treating early prostate cancer. A comprehensive review of all approaches used in the management of early/localized prostate cancer was presented in FO, pp 292-298.

SURGERY VERSUS BRACHYTHERAPY

One of the controversies emerging in the treatment of localized prostate cancer involves brachytherapy, a procedure that uses temporary or implantable radioactive sources (seeds) for interstitial irradiation of the prostate. In the past, like with most other cancers, early disease has been traditionally treated by surgery to remove the gland, or with external beam irradiation when surgery was contraindicated. However, because of devastating complications associated with radical prostatectomy, other approaches have been developed that appear to offer a less traumatic means of achieving a similar long-term effect with a significantly lower incidence of the two most dreaded side effects, namely impotence and incontinence. In the past, external beam radiotherapy was put forth as such an option but a significantly lower survival rate at five and ten years has reserved this approach for those unable or unwilling to undergo prostatectomy. Recently, another radiotherapy approach, brachytherapy, has been gaining ground based on positive reports both from anecdotal input from patients and from several long-term follow-up studies. However, brachytherapy is generating considerable controversy among physicians with a turf war brewing between surgeons and radiation oncologists with the patient left to decide for himself.

Recently, a number of studies have been released comparing radiotherapy (external beam radiotherapy and/or brachytherapy) with surgery for the treatment of localized disease. According to a recently published study (Talcott J, etal, J Clinical Oncology 1998; 16:275-283), complication rates of bowel, urinary and erectile dysfunction following radical prostatectomy or external beam radiotherapy for prostate cancer, are substantially higher than reported in previous studies. In a prospective study of 279 patients with prostate cancer who underwent either radiotherapy (n=135) or radical prostatectomy (n=125, with attempted nerve preservation in two-thirds), self-reported patient data was collected before treatment, as well as 3 and 12 months after treatment. Symptoms reported by patients, in the first year after either radical prostatectomy or external beam radiotherapy, included high rates of irritative bowel and bladder, urinary incontinence, and erectile dysfunction. Diarrhea, rectal urgency, and daytime urinary frequency each occurred in about 25% of patients at 3 months following radiotherapy but subsided "somewhat" by 12 months. Substantial urinary incontinence was reported by 11%, and absorptive pad use by 35% of patients.

The before and after incidence of inadequate erections was 23% and 91% for surgery patients, and 33% and 61% for radiotherapy patients.

Radical Prostatectomy

Radical prostatectomy is used routinely to treat early-stage prostate cancer in young healthy males. It has been assumed that development of better surgical approaches, intended to preserve nerve function, have helped diminish the rate of serious post-surgical complications such as impotence and incontinence. However, recently released studies indicate that this is not the case. Incontinence requiring diapers may occur in 5%-10% of cases, and some amount of dribbling or minor incontinence can occur in another 20%. Impotence is even more frequent, occurring 60%-80% of the time but use of nerve-sparing (NS) prostatectomy for some patients with very early stage cancers, may reduce the impotence rate to about 30%. Also, radical prostatectomy is a major surgery, associated with such possible problems, as prolonged recovery, blood clots, infection, bleeding, heart problems, or pneumonia.

Nerve-sparing (NS) prostatectomy, particularly when unilateral, may not preserve sexual function as well as previously thought and may increase urinary incontinence, as reported in a recent study (Talbott JA, etal, JNCI, 6 Aug 1997; 89(15):1117-1123). Among 94 patients (median age=62) with early prostate cancer who underwent either non-NS (28 patients), unilateral NS (38 patients), or bilateral NS (28 patients) surgery, performed by 35 different surgeons, those treated with NS radical prostatectomy were younger with fewer comorbid diseases and less advanced cancers, particularly those who underwent the bilateral procedure. Despite the large number of surgeons involved, it was determined that the results were not influenced by any variations in their qualifications/experience.

Before surgery, 25% of those treated with non-NS surgery were completely impotent, and 75% had erections considered inadequate for sexual intercourse compared to only 8% and 19%, respectively, among those who underwent nerve-sparing surgery. However, more than two thirds of those who reported data on sexual function, irrespective of type of surgery, were completely impotent at 12 months and only 4 of the 37 (11%) who underwent NS surgery were fully potent at 12 months. Total and partial impotence rates of those who underwent unilateral NS surgery were identical, 83% and 100%, respectively, to those who underwent non-NS surgery. Those who underwent bilateral NS surgery reported complete impotence less often, but few had firm enough erections for successful sexual intercourse. Eleven of 19 patients (58%) with preoperative sustainable erections who underwent bilateral NS, had erections at 12 months, but only in 21% of cases erections were usually adequate for sexual intercourse.

Prior to surgery, the frequency of urinary incontinence was low in all patients. However, more patients in the NS surgery group reported leaking urine and/or the need to wear absorbent pads compared with those in the non-NS surgery group. Patients who underwent bilateral NS surgery reported fewer postoperative problems related to urinary incontinence compared with those who underwent unilateral NS surgery.

One explanation why this study's results differ from other trials may be the fact that the information was collected by independent observers and patients were asked to fill out questionnaires anonymously. When asked by their caregivers, patients may be reluctant or embarrassed to reveal sexual or incontinence problems. Although these findings were criticized by Patrick C. Walsh, MD, who pioneered the NS procedure and performs 200 such procedures annually, they were applauded by others as being more representative of the real world. However, the study involved only a small sample of preoperatively potent men (18) who underwent bilateral NS surgery, followed for one year; potency was 20% in this group. Dr. Walsh attributed the disappointing study results to the fact that nerves were not spared because of surgeon inexperience, as indicated by the high rates of both incontinence and impotence. However, many practitioners believe that these findings illustrate the high risk of lifelong disabilities associated with radical prostatectomy as currently performed by many surgeons.

UroMed (Needham, MA) is marketing CaverMap, a surgical aid to assist surgeons in locating and stimulating the critical cavernosal nerves during prostate surgery. It is believed that, by identifying and locating the cavernosal nerves, a skilled surgeon may potentially be able to preserve nerves to prevent impotence. The product was approved by the FDA in November 1997.

Radiotherapy/Brachytherapy

Radiation therapy, mainly brachytherapy, has been gaining ground as an alternative to surgery. Traditionally, radiotherapy has not been considered as effective as surgery, based on 5- and 10-year survival rate comparisons. In a retrospective analysis of outcomes of 999 patients treated with megavoltage radiation between 1970-1985, 10-year survival was dependent on stage (Duncan W, etal, Int'l J Rad Onc, Bio, Phys, 1993, 26(2):203-210):

Stage at Diagnosis	% Survived at 10 years
T1	79
T2	66
T3	55
T4	22

Use of 3D conformal radiation therapy is becoming popular as an alternative to radical prostatectomy in early stage prostate cancer because it minimizes exposure of healthy tissue to external beam radiation without compromising effectiveness. Results from a study conducted at the University of Michigan Health System (Ann Arbor, MI) suggest that disease control equivalent to radical prostatecto-

Exhibit 1
Estimated Prostate Cancer Populations by Stage at Time of Diagnosis in Selected World Regions in 1998

Stage	Total (%)*	USA (#)	North America (#)	Europe (#)	Japan (#)	Former USSR (#)	Triad (#)
Localized	57	105,165	113,630	121,898	9,792	22,581	245,319
Regional	17	31,365	33,890	36,356	2,920	6,735	73,165
Distant	14	25,830	27,909	29,940	2,405	5,546	60,254
Unstaged	12	22,140	23,922	25,663	2,061	4,754	51,646
All Stages	100	184,500	199,350	213,856	17,179	39,616	430,385

** Based on SEER data*

my can be achieved with 3D conformal radiation therapy. This study focused on a consecutive series of 172 patients with early stage prostate cancer. The criteria for the study was disease Stage T1 or T2, PSA≤10 ng/ml, Gleason score ≤7, and age≤70 years. Therapy was conformal and was designed to provide complete dosimetric coverage of the treatment target. The overall survival rate at 5-8 years was 95% with 5 deaths, none attributable to prostate cancer. Freedom from biochemical recurrence at 5-8 years was 85% with a total of 13 biochemical failures. These results indicate that at least out to 8 years, freedom from biochemical recurrence is as good as that achievable with surgery (Sandler HM, etal, ASCO98 Abs. 1184:307a).

Brachytherapy, a procedure that may be defined as a localized sustained delivery of radiation therapy via permanently or temporarily implantable radioactive sources, is being attempted in a variety of configurations for various cancers and other diseases. Radioactive seeds may be implanted in a variety of sites via interstitial, intravascular, intracavitary and intraluminal routes. In addition to prostate cancer, brachytherapy is used in breast, lung, bronchial, head and neck, esophageal, biliary and bladder cancer, brain tumors, hepatocellular carcinoma and various gynecologic malignancies such as ovarian, endometrial and cervical cancer, among others.

One of the most attractive aspects of brachytherapy is that it offers patients a quality of life (QoL) superior to that of radical prostatectomy or external beam radiotherapy. According to V. Elayne Arterbery, MD, director of the Critten DMC Radiation Oncology Center (Rochester, MI) and associate professor at Wayne State University (Detroit, MI), as reported in a poster session at the 1998 meeting of the American Society of Therapeutic Radiology and Oncology (ASTRO), among 51 consecutive patients with clinically localized prostate cancer (Stage T1c or T2b) who underwent brachytherapy with either iodine-125 (^{125}I) or palladium-103 (^{103}P) seed implants from September 1995 to October 1996, 87% were sexually potent 6 months after the implant with 74% experiencing a similar level of sexual activity as before the implant. At 6 months, 40% of patients urinated more frequently than before the procedure, and 17% experienced mild pain or burning upon urination. None of the patients reported hematuria, and only 3% had any difficulty controlling urinary flow. Only 3% of the men felt that their symptoms disrupted their family life, none reported any psychological distress, and most returned to work within 3 days. Post-implant, most of the men (93%) said they took alpha blockers for 6 weeks, and 75% felt that the drugs improved their symptoms.

According to John C. Blasko, MD, professor of radiation oncology at the University of Washington School of Medicine (Seattle, WA) and brachytherapy proponent, brachytherapy may be the simplest, least expensive, and best tolerated treatment available for early stage prostate cancer and, for locally advanced disease, adding brachytherapy to external beam radiotherapy may enhance the intraprostatic effects of radiation without excessive extraprostatic tissue toxicity. In Dr. Blasko's experience, brachytherapy has been equivalent to radical prostatectomy and external beam irradiation in the treatment of localized prostate cancer. Among 320 consecutive men with prostate cancer (Stage T1b or T2a-b, Gleason score=2 to 7, initial median PSA level=7.9 ng/ml, and average age=70 years), at 7 years post-treatment, 97% exhibited local control of the disease, 95% were free of distant metastases, 92% were free of prostate cancer, and 99% had not died from cancer. Also, brachytherapy, in combination with external beam irradiation, was shown to be superior to conventional external beam irradiation alone for men with locally advanced prostate cancer (Stage T1b to T3). At 96 months post-treatment, among 232 consecutive men (36% with Gleason scores >6 and a mean PSA level of 15.6 ng/ml), local control of prostate cancer was maintained by 91%, 83% had no distant metastases, 74% were disease-free, and 96% had not died of cancer.

Others, however, believe that the jury is still out on brachytherapy because there is insufficient long-term data on the effectiveness of this procedure. Also comparisons based on certain patient characteristics may be misleading because no randomized studies have been performed comparing the various options in highly controlled situations.

Nevertheless, brachytherapy has been gaining ground as an alternative to radical prostatectomy and industry sources estimate that approximately 50,000 such procedures would be performed annually in the USA for prostate cancer alone. Judging from Medicare data estimating the

Exhibit 2
Estimated Five-Year Prostate Cancer Survival by Stage Determined at Time of Diagnosis in Selected World Regions in 1998

Stage	Total (%)*	USA (#)	North America (#)	Europe (#)	Japan (#)	Former USSR (#)	Triad (#)
Localized	99	103,840	112,198	120,362	9,669	22,297	242,228
Regional	92	28,931	31,260	33,534	2,694	6,212	67,488
Distant	30	7,734	8,356	8,964	720	1,661	18,040
Unstaged	80	17,610	19,028	20,412	1,640	3,781	41,079
All Stages	86	158,115	170,841	183,272	14,722	33,951	368,836

** Based on SEER data*

number of prostatectomies performed in 1996 (Exhibit 3), this estimate represents a major increase from historic levels.

Brachytherapy costs compare favorably with those associated with other procedures, especially when all outlays are considered, including hospitalization costs for surgery and multiple visits for external beam radiotherapy. These costs are covered by Medicare and by most insurance companies.

The current USA market for permanent radioactive seeds, used in all applications, is approximately $60 million. Ironically, brachytherapy is now competing with radical prostatectomy and external beam techniques, the same approaches that contributed to a waning of interest in brachytherapy in the past. Treatment configurations by disease profile are listed in Exhibit 4. Commercially available brachytherapy seeds and systems are described in Exhibit 5.

Permanent interstitial implant brachytherapy, a technique first attempted in 1911 and used with marginal success in the 1940s, was later discarded because of poor results. It seems that the freehand placement of the seeds in an open surgical procedure, was not uniform enough, leaving "cold spots" between implants and, consequently, the tumor was not completely eradicated. Seed brachytherapy was rejuvenated in the 1980s with the advent of better guidance techniques such as transrectal ultrasound (TRUS) and CT imaging, that provide detailed and precise measurements of prostate size and shape to aid both in treatment planning and in accurate placement of the seeds under full procedural guidance. Distribution of radiation dose can also now be verified after the implantation by CT scans or X-rays.

Permanent seed implantation involves placement of tiny pellets containing radioactive material into the prostate under ultrasound guidance. This technique allows the delivery of a highly concentrated, yet confined, dose of radiation directly to the prostate. Because the radiation is delivered locally to the tumor, normal tissues are spared excessive radiation exposure.

Brachytherapy currently relies heavily on computerized planning to eliminate any variations in targeting the whole gland. Before the procedure, ultrasound scans are used to create a map of the prostate to design a treatment plan that calculates the exact number of seeds for complete coverage and accurate placement. This plan is then validated by using a treatment planning computer that constructs the implant model which is reproduced during treatment using an ultrasound probe positioned in the rectum to monitor proper needle alignment. A template guidance device with holes that correspond to the grid on the ultrasound computer screen, is used to guide the introduction of implant needles through the appropriate template holes, as indicated in the treatment plan. Each needle is guided through the template, and then through the perineum to a predetermined position within the prostate under direct ultrasound visualization. Needles may be preloaded with seeds or may be attached to an applicator that dispenses the seeds through the needle into the prostate. A predetermined number of seeds, about 100 in all, are implanted as each needle is withdrawn from the prostate. When all the seeds have been inserted, the ultrasound image is again reviewed to verify seed placement.

Physicians generally perform the 60-90 minute procedure in an outpatient setting under spinal or general anesthesia, and patients are able to return home the same day with few side effects. Most normal activities can be resumed within 48 hours following treatment. Reported complications include some bruising and swelling between the legs which disappears within a few days. Longer lasting symptoms that wane as the seeds lose their radioactivity and typically require no medical intervention for most patients, may include different degrees of urinary discomfort such as frequent urination, a sense of urgency when urinating, a slower urinary stream and, sometimes, a burning sensation during urination. Slight bleeding or blood in the urine may also occur in the first weeks after the procedure. Rectal complications are rare and are characterized by bouts of rectal irritation and occasional rectal bleeding. These symptoms that may be treated with medication, generally subside in less than three months. Incontinence is rarely a concern in patients who have not had prior urinary tract surgery. According to a survey of 400 patients treated with brachytherapy, conducted by the Northwest Tumor Institute (Seattle, WA), 85% of those <70 years-of-age who were potent prior to the procedure

remained potent. Among those over the age of 70, 50% retained potency.

In April 1998, results reported by Northwest Hospital (Seattle, WA) indicated that, ten years after treatment for early-stage prostate cancer, 66% of patients treated with permanent seed brachytherapy remained disease-free based on a PSA level of 0.5 ng/ml or less, clinical examination and prostate puncture biopsy results. The study involved 152 patients with stage T1 to T3 prostate cancer who underwent this procedure, with or without additional external beam radiation, between January 1987 and June 1988. Although these results appear favorable, they are not as good as those achievable with radical prostatectomy in highly selected groups of younger patients with stage T1 disease that approach a 10-year progression-free survival of 85-90%.

Brachytherapy may also be used in patients who previously underwent a transurethral resection of the prostate (TURP) that changes the geography of the prostate gland and may interfere with uniform placement of seeds. A closer look at the overall incidence of incontinence in 14 of 274 patients, (average follow-up of 40 months), treated at the Northwest Tumor Institute, shows that 90 of the 274 patients had a prior TURP. Incontinence developed in 14 of those 90, or 16%. None of the other 184 patients without TURP developed incontinence. Also, presence of a previous TURP did not interfere with the safety and efficacy of combination of external beam radiation therapy, followed by brachytherapy, in the treatment of localized prostate cancer.

The primary radiation sources used in permanent seed brachytherapy are ^{125}I and ^{103}P (Exhibit 4) and most of the results described above involve use of these sources. Both ^{125}I and ^{103}P are low-energy sources and the shorter half-life of ^{103}P has made it more popular than ^{125}I for permanent brachytherapy. However, there is another source, gold-198 (^{198}Au), that has been used at Baylor College of Medicine (Houston, TX) since 1965 for prostate cancer brachytherapy. ^{198}Au is a high-energy source with a half-life of only 2.7 days. Justification for its use is more effective coverage of the prostate gland with fewer seed implants. Usually about 40 ^{198}Au seeds are placed in the periphery of the gland compared to the 100 ^{125}I or ^{103}P seeds needed to be placed throughout the gland, and accurate placement of ^{198}Au seeds is not as important as is with ^{125}I or ^{103}P seeds. Also, ^{198}Au implants are smaller and may be considered as point sources and are not associated with the anisotropy encountered in larger seeds that complicate dosimetry calculations.

Although it is too early to assess the survival impact of ^{198}Au brachytherapy among 54 patients treated between 1992 and 1996 with ^{198}Au implants, followed by external beam radiotherapy, to date, there were 3 treatment failures. Proctitis occurred in 59.9%, urethritis in 39.5%, and cystitis in 37.7%. Among 30 patients with locoregional prostate cancer who failed initial combined brachytherapy and external beam radiation therapy, treated between 1990 and 1996, 25 failed treatment. Among the five responders, the mean disease-free survival was 33.8 months (Butler EB, etal, Seminars in Surgical Oncology 1997, 13:406-418).

High-dose-rate (HDR) temporary brachytherapy, is a newer brachytherapy modality gaining ground for treatment of locoregional prostate cancer. HDR temporary brachytherapy involves inserting approximately 16 tiny flexible plastic catheters into the prostate gland in the operating room and, using a computer-controlled dispenser, single highly radioactive iridium-192 (^{192}Ir) seeds are pushed into the catheters one by one. The patient remains in the hospital for the next 30 hours and is brought into the radiation oncology department 3-4 times, for a 5-minute brachytherapy treatment or longer, as deemed necessary to deliver the necessary radiation dose in a given region of the prostate. Radiation is delivered at doses of 500cGy to 700 cGy at a rate of 20-50 cGy min. This ability to vary the radiation dose within the prostate is one of the advantages of HDR temporary brachytherapy. After the final treatment, the catheters are removed, and the patient is discharged. This approach is generally combined with low-dose external beam radiation and short-term hormonal therapy for a three-pronged attack on prostate cancer to kill cancer cells that may have migrated outside the prostate gland (extracapsular spread).

Unlike permanent seeding alone which is recommended for very early prostate tumors, HDR temporary brachytherapy in combination with external beam irradiation and/or hormonal therapy, can be used for a wide range of prostate cancer stages, PSA values, and tumor grades, and may be even used for tumors which are considered too advanced for radical prostatectomy, as long as there is no obvious distant metastases. When external beam radiation alone was compared in combination with HDR temporary brachytherapy in patients with locally advanced prostate cancer (Stage T2b through T3c), at three years the cancer control rate was 85% versus 52% in favor of brachytherapy (Stromberg, etal, Cancer J Sci Am 1997;3:346-352).

Complications such as impotence may occur 20-30% of the time, but incontinence has not been reported to occur with this protocol. Burning urination that sometimes occurs is less severe than with permanent seed implants and may last only for a few weeks or a few months. Mild rectal irritation may also occur during the period of external beam irradiation. Urinary blockage may be caused by swelling of the prostate, or by formation of a stricture in the urethra.

HORMONAL THERAPY

Hormonal therapy for prostate cancer has been discussed extensively in FO, pp 303-307. Adjuvant long-term hormonal therapy has been a standard management approach for hormone-dependent prostate cancer. Hormonal therapy has also been shown effective in the neoadjuvant setting in combination with surgery or radiotherapy. Recent studies have shown that adding hormonal therapy to radiation can significantly increase cancer control rates. Reports from Europe also indicate that adding an

LHRH analog regimen to radiation therapy when treatment is initiated, and continuing the hormonal regimen for the next three years, produces a more favorable outcome than radiotherapy alone.

In a phase III clinical trial, use of androgen suppressing drugs in conjunction with radiation therapy enhanced tumor control in cases of advanced prostate cancer. Patients with large Stage T2-T4 tumors with no evidence of metastases, were randomized and treated with goserelin (Zoladex; Zeneca) (3.6 mg) every 4 weeks and flutamide (Eulexin; Schering-Plough) (250 mg) *tid* for 2 months prior and during radiation therapy (arm I). A second group (arm II) was treated with radiation therapy alone. Results indicate that application of a brief course of androgen deprivation in conjunction with definitive radiotherapy is associated with a significant improvement in local control and reduction in disease progression. However, the observed improvement in survival has not reached statistical significance (Pilepich MV, etal, ASCO98, Abs. 1185:308a).

Exhibit 3
Selected Prostate-related Procedures Performed on Male Medicare Recipients in 1996

Procedure	CPT-1997 Code	Total Procedures (#)	Total Cost ($)	Average Cost per Procedure[1] ($)
Biopsy	55700-55705	274,734	71,640,427	260.76
Prostatectomy	52601	121,221	215,086,937	1,774.34
Laser procedure for vaporization[2]	52648	6,406	10,112,102	1,578.54
Brachytherapy	55859	4,336	6,208,078	1,431.75
Laser procedure for coagulation[2]	52647	1,921	2,984,466	1,553.60

[1] Medicare reimbursement rate varies from 42.3% to 57.1% of these costs
[2] Mostly for benign prostatic hyperplasia (BPH)
Source: HCFA Database, 1996

Although both surgical or chemically-induced castration are devastating alternatives in prostate cancer treatment, drug treatment may be preferable to surgical castration in advanced prostate cancer. In a survey of patients with advanced prostate cancer (n=1,285) who were treated with either bicalutamide (Casodex; Zeneca) (150 mg) monotherapy or castration in two separate trials, objective responses favored Casodex. Combined analysis involving 288 patients with metastatic cancer who were symptomatic at entry and, therefore, evaluable for response, showed that 70% of those randomized to Casodex and 58% to castration experienced a response. There was a statistically significant difference in favor of Casodex for best subjective response. Regarding survival, there was a small but significant advantage for castration with a six weeks difference in median survival (Casodex 105 weeks and castration 111 weeks) in M1 patients (n=805) but in M0 patients (n=480) survival was equivalent for the two treatment groups (Tyrrell CJ, etal, ASCO98, Abs. 1214:315a).

However, the value of combined androgen ablation does not appear to add any benefit in advanced prostate cancer. Patients treated with orchiectomy do not fare better when also placed on a flutamide regimen. In a large prospective clinical trial 1,387 patients with confirmed Stage D prostate cancer who underwent surgical castration, were randomized to flutamide (250 mg) *tid* or placebo. Adding flutamide to surgical castration did not improve time to disease progression (21 months for the flutamide group compared to 18 months) but within a "good risk" sub-group, it was 49 months versus 36 months. Survival was 31 months on flutamide compared to 30 months on placebo; it was 52 and 51 months, respectively, in the "good risk" subgroup (Crawford ED, etal, J Urol 1997, Abs. 1311, 157:336). Although results of this study indicate that this type of combined androgen ablation does not seem to favorably affect outcome and only adds to the cost and side effects of treatment, other combinations, for instance a leuprolide (Lupron; TAP Pharmaceuticals) and flutamide combination, has produced more favorable results than leuprolide monotherapy.

Traditionally, it was thought that hormonal approaches did not have a role in metastatic prostate cancer that progresses after androgen deprivation (hormone-refractory). However, many patients who progress in this setting are still hormone-sensitive. Use of flutamide as second-line therapy in progressive metastatic disease is associated with an overall response rate of 35%, consisting of objective response rate of 15% and disease stabilization rate of 20%. It also appears that flutamide, bicalutamide and perhaps nilutamide (Nilandron; Hoechst Marion Roussel) are not cross resistant and each may prove effective in some patient when the other one fails.

CHEMOTHERAPY

It was widely held in the past that advanced prostate cancer does not respond to chemotherapy. However, several new approaches, designed to take into account the molecular factors involved in the progression of prostate cancer, may provide effective chemotherapy treatments in advanced, metastatic disease. Several combinations show promise in this difficult to treat disease (see Exhibit 6).

Estramustine

One agent with demonstrated limited activity in advanced hormone-refractory prostate cancer is estramustine (Emcyt; Pharmacia & Upjohn), a nor-nitrogen mustard

Exhibit 4
Brachytherapy Sources and Treatment Parameters

Products		Patient Characteristics			Treatment
Brachytherapy Source	**Half-life/Energy**	**Tumor Stage**	**Gleason Grade**	**PSA Level**	**Adjunct Procedures**
Iodine-125 (0.3 mCi-0.9 mCi)	60 days/28 KeV	=T2a	=7	=10 ng/ml	If prostate volume is >40 cc, pre-operative androgen ablation therapy is administered for 3-6 months
Palladium-103 or Iodine-125	17 days/22 KeV	T2b, T2c, or T3a	>7	>10-<30 ng/ml	External beam irradiation and 3-6 months of androgen ablation therapy resulting in a gland volume of <40 cc
Gold-198 (^{198}Au)	2.7 days/412 KeV	T1, T2, T3 or patients who relapsed after first brachytherapy	=5.8	=9.2 ng/ml	All patients were treated with external beam radiotherapy
HDR temporary brachytherapy using iridium-192		T1-T4	Any	Any	Almost any size prostate gland is acceptable; extremely large glands may require longer hormone therapy consisting of a once-a-month (or once-every-three-month) injection of Lupron, and once-a-day Casodex, initiated 3 months before brachytherapy, and continued for 3 months afterwards; two weeks after the implant, 4-5 weeks of conformal external beam radiotherapy are administered

linked to an estrogen. Estramustine acts by depolymerizing cytoplasmic microtubules, binding to microtubule-associated proteins, inhibiting P-gp and disrupting the nuclear matrix (Petrylak GB, etal, ASCO98, Abs. 50:62). Estramustine may be more effective when used in combination with other agents, including docetaxel.

Mitoxantrone

Combination chemotherapy using mitoxantrone (Novantrone; Immunex) and hydrocortisone results in a 33% decline in PSA and 10-15% objective response rate in hormone-refractory prostate cancer. Also, this combination relieves pain associated with bone metastases and delays time to tumor progression, as is the case with strontium-89 (^{89}Sr, Metastron; Nycomed Amersham) which has a synergistic antitumor activity. In a previously untested combination, ^{89}Sr (4 mCi) was administered IV every 12 weeks in combination with IV mitoxantrone (10, 12, 14 and 16 mg/m^2), every three weeks, beginning on day 22, along with daily PO hydrocortisone (40 mg), in patients failing hormone ablation antiandrogen withdrawal who had prior therapy but no prior exposure to ^{89}Sr, mitoxantrone or doxorubicin. Among the first 10 patients treated with mitoxantrone at the 10 mg/m^2 dose level, all experienced 100% pain relief and 8 evaluable patients experienced pain relief and all stopped narcotics. Also, PSA declined (81%, 87% and 94%) in 3 of 8 patients. Disease progressed rapidly in 2 patients and stabilized in 3. Among 9 patients evaluable for toxicity, DLT was encountered in 3 with progressive or stabilized disease, manifested as persistent Grade 2 platelet toxicity. Two of these patients were found to have bone marrow metastases. There was no Grade 4 toxicity. This regimen is active, but chronic thrombocytopenia may be DLT (Cohn H, etal, ASCO98, Abs. 1265:328a).

Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF)

Immunotherapy using GM-CSF (sargramostim, Leukine; Immunex) has also been attempted in a phase II clinical trial in patients with metastatic hormone-refractory prostate cancer. The rationale in using this approach is based on the observation that GM-CSF enhances an antitumor immune response through direct activation of dendritic cells and macrophages and indirect T cell activation via IL-1 and TNF. In the Dunning rat prostate carcinoma model, treatment with irradiated prostate cancer cells, engineered to secrete human GM-CSF, resulted in a longer disease free survival compared to controls. GM-CSF (250 µg/m^2) was administered subcutaneously on days 1 to 14, every 28 days, in 22 patients (11/22 had measurable disease and 21/22 had a positive bone scan; 13/22 had prior chemotherapy; and 21/22 had 3 or more prior hormonal treatments), after the antiandrogen withdrawal effect was excluded. Median PSA before initiation of GM-CSF was 276 ng/ml. PSA declined in 10/22 patients after 2 weeks on GM-CSF, but climbed back again during the off-therapy period. Median maximal PSA decline was 37% (range=5.8% to 64%) and in 5/22 patients the PSA decline was ≥50%. Median PSA response duration was 4.0 months. Because in

an *in vitro* system, using an androgen-independent cell line, GM-CSF did not result in diminished PSA production per cell compared to control, it appears that decreased PSA levels in these patients is not attributable to suppression of PSA production alone but that the effect of GM-CSF on PSA may be biologically significant. A trial of GM-CSF in less heavily pretreated patients with a smaller tumor burden is warranted (Whisenant S, etal, ASCO98, Abs. 1343:348a).

CHEMOPREVENTION

Prostate cancer is an ideal target for chemoprevention because it is a slowly developing malignancy that originally manifests itself in a latent form as early as in a man's late twenties (also see FO, p 289). However, a viable chemopreventive for prostate cancer has not been identified to date. There are several candidates (see FO, p 288), among them finasteride (Proscar; Merck) that is being evaluated in an NCI-sponsored trial initiated in 1993. Enrollment in the $60 million Proscar trial closed in December 1996, after 18,000 men were enrolled. Interestingly, misreported news that Proscar was useless in BPH (this result was only valid for small prostates) prompted 10% of the study's participants to quit, although the news were in no way related to prostate cancer.

Next issue: *Novel treatments for prostate cancer, including a database of over 150 agents in development.*

SPECIAL MID-YEAR REVIEW

OVERVIEW OF ONCOLOGY TRENDS — PART I

The oncology landscape has been undergoing a major transformation in the late 1990s. Several reasons for these changes are shown in Exhibit 7. However, a cancer cure remains elusive despite pronouncements to the contrary by the popular press that frustrate scientists and caregivers alike and confuse the public. Actually, despite the availability of costly second- and third-line treatments, the fate of cancer patients with advanced malignancies is grim. For instance, in reviewing the outcome of 377 patients with refractory metastatic/locally-advanced breast cancer who were treated with docetaxel in 1995, in the community setting in 61 British cancer units under a compassionate use program, only 26 (6.7%) patients, and none with CR, were still alive 2 years later. Median survival of all patients was 194 days. Of the 151 patients who experienced an objective response, median survival was 312 days; for those with CR it was 358 days. Survival of responders was 41% at 1 year and 13% at 2 years. Median survival for nonresponders was 54 days (Leonard RC, ASCO98, Abs. 434:112a).

There is considerable controversy as to where we stand today in the war against cancer, over a quarter of a century and $36 billion later. Pessimists state that we have not come very far and their point is well taken when one considers the annual toll. Optimists, on the other hand, bring up lives saved as the true measure of the effort as well as the incredible knowledge amassed during these years. Of course, both sides are partly right and the result to date is a mixed bag with the promise to conquer cancer still sometime in the future. Nevertheless, availability of second- and third-line treatments have extended patients lives. Also, better management of side effects has made palliative care possible and improved the quality of life (QoL) of terminal patients.

Undoubtedly, these are heady times for those participating in the cancer field, be it academics, practicing oncologists, developers of commercial products and even patients. Knowledge is advancing so rapidly that it is difficult to evaluate its impact in the real world. In the laboratory, millions of mice have being cured of a variety of cancers. Also, there are numerous anecdotal cases of patients being cured by one approach or another but, to date, not one agent that has been tested in humans generated an overwhelming positive result in any one clinical situation. Numerous problems, from the obvious, as sheer size, to the complex, as pharmacokinetics, toxicity and drug resistance, among others, have conspired to make the transition from mice to men truly unpredictable. Nevertheless, despite the critics, history be will kinder to the contributions of this decade to the war on cancer.

This review is based on reports from the 1998 annual meetings of the American Association for Cancer Research (AACR) which took place in March 1998 in New Orleans, LA, and the American Society of Clinical Oncology which took place in May 1998 in Los Angeles, CA, as well as NEW MEDICINE'S Oncology KnowledgeBASE (nm|OK), an electronic resource in the cancer field, and many other sources.

NEW CHEMOTHERAPEUTICS TAKE OFF

Chemotherapy agents are becoming serious revenue generators. The incredible success of Taxol that became a blockbuster drug within a couple of years after its market introduction, has encouraged many pharmaceutical companies to look to the cancer field as a potential major worldwide market opportunity. Worldwide sales of selected new chemotherapeutics and some adjuncts used in cancer treatment, in 1997, are estimated in Exhibit 8.

Topoisomerase I Inhibitors

Use of topoisomerase I (topo I) inhibitors continues to expand as numerous clinical trials are underway to evaluate these agents in a variety of malignancies, alone or in combination with other chemotherapeutics. For a comprehensive review of topo I inhibitors see FO, pp 528-544. According to nm|OK, in addition to those approved and launched worldwide, there are currently more than 20 drugs/formulations that inhibit either topo I or topo I and II in preclinical and early stages of clinical development.

Exhibit 5
Manufacturers and Developers of Brachytherapy-related Products

Manufacturer	Product	Comments
Imagyn Medical Technologies (IMT; was Urohealth; Newport Beach, CA)	^{125}I or ^{103}P	In January 1998, IMT signed a contract agreement with International Isotopes (I^3; Denton, TX) granting IMT an exclusive, worldwide license to market ^{125}I and ^{103}P seeds, for the treatment of cancer and other diseases. IMT has made a commitment to pay I^3 up to $1 million and also provide I^3 with a minimum three-year supply contract for ^{125}I seeds valued at several million dollars. In June 1998, I^3 signed an agreement with EndoTech (Spokane, WA) to obtain worldwide rights to U.S. patent #5,342,383 (4/94) and an FDA 510K marketing approval for ^{125}I spherical encapsulated brachytherapy seeds that are manufactured using sputter coating technology
North American Scientific (North Hollywood, CA)	IoGold ^{125}I	Second generation ^{125}I implant approved by the FDA in February 1997; to be marketed by Mentor (Santa Barbara, CA)
Nucletron (Veenendaal, The Netherlands and Columbia, MD)	Integrated Brachytherapy Unit (IBU)	The IBU integrates all aspects of HDR brachytherapy, the operation and the consecutive implantation and irradiation, in a single procedure. IBU incorporates an X-ray monitor and PLATO planning monitor; a treatment table optimized for brachytherapy surgery and imaging; an isocentric X-ray gantry to makes images for planning, and fluoroscopy for viewing catheters and implants; the microSelectron-HDR for treatment directly following planning; and an anesthesia unit and all other equipment needed to assist in surgery procedures
Nycomed Amersham	Rapidstrands ^{125}I	In 1997 overall sales of Rapistrauds ^{125}I seeds were $32.3 million
Sauerwein (Haan, Germany)	GAMMAMED 12iT	A trasportable HDR afterloading system for intravascular irradiation, the GAMMAMED 12iT has 24 channels and is designed for use at a single site; uses ABACUS treatment planning interface
Siemens Medical Systems, Ultrasound Group (Issaquah, WA)	SONOLINE Prima with a transperineal guidance kit	Allows the SONOLINE Prima ultrasound system to be used in brachytherapy applications by facilitating needle placement
Theragenics (Norcross, GA)	TheraSeed-Pd103	TheraSeed-Pd103, introduced in 1986, is a rice-sized titanium capsule that contains ^{103}P. Sales of TheraSeed increased 98.4% to $24.6 million in 1997, compared to $12.4 million in 1996. In May 1997, Theragenics licensed exclusive worldwide marketing rights of TheraSeed to Indigo Medical (Cincinnati, OH), a subsidiary of Johnson & Johnson (J&J). Indigo is responsible for the promotion, sales and marketing of TheraSeed and Theragenics for manufacturing manufacturing and distribution. The agreement is effective for seven years, and may be extended for three years thereafter. As part of this collaboration, J&J also acquired $5 million of Theragenics common stock. In January 1998, Theragenics announced it has entered into an agreement to purchase six additional cyclotrons used to produce TheraSeed. All six cyclotrons are scheduled to be on line by the end of 1999 in anticipation of increases in TheraSeed demand generated by Indigo. With the completion of this purchase, Theragenics will have 14 cyclotrons in place by the end of 1999. In June 1998, Theragenics announced that it obtained a CE Mark to market TheraSeed in the 15 member countries of the European Union
UroMed (Needham, MA)	^{125}I brachytherapy seeds and insertion needles	In March 1998, UroMed entered into an exclusive licensing agreement with BEBIG (Berlin, Germany) to market the latter's ^{125}I seed for prostate cancer treatment in North and South America and non-exclusive rights outside this area. The term of the agreement is 6 1/2 years from the date seeds are available for sale, and provides for continuous three-year renewals as well as rights to assure UroMed's continued participation in the business if the agreement is not renewed. The agreement calls for a total commitment by UroMed of approximately $1.75 million in milestone payments to be made when BEBIG's performance goals are met. These milestone payments will be used to support the construction of the production line. A portion of the $1.75 million payment will be treated as an advance against future seed purchases. BEBIG will contribute $1.25 million to the funding of the production line, which will have an estimated annual capacity of 500,000 seeds. At the 1998 American Urological Association (AUA) annual meeting, UroMed introduced a product line consisting of insertion needles used as introducers for radioactive brachytherapy seeds used to treat prostate cancer
Varian Oncology Systems (Palo Alto, CA)	VariSource HDR Brachytherapy System	VariSource uses thin catheters and needles, often less than half the size of needles used by other manufacturers, and allows access to tumors that were previously untreatable with brachytherapy. An extremely small source diameter makes VariSource ideal for interstitial techniques, resulting in significantly reduced patient trauma. VariSource's line source geometry ensures uniform dose distribution, avoiding the scalloped isodose shape common in point source configurations

Topotecan (Hycamtin; SmithKline Beecham), approved as second-line chemotherapy for the treatment of ovarian cancer, took off in 1997, posting global sales of $85 million, up 104% from comparable 1996 levels. Sales in the first quarter of 1998 were $26,000,000, up 51% from the comparable 1997 period; USA sales were $18 million, up 12%. In 1997, the AWP of one cycle of topotecan was $2,250. The approved administration route is IV infusion but both intraperitoneal and oral routes are being clinically investigated.

Topotecan may compete head on with paclitaxel as first-line treatment of advanced ovarian cancer. In a multicenter, randomized, phase III clinical trial involving 226 patients with advanced epithelial ovarian cancer who had failed one prior platinum-based regimen, 112 patients were treated with topotecan and 114 with paclitaxel; of these, 61 were switched to topotecan and 49 to paclitaxel. Topotecan (1.5 mg/m^2) was administered daily for 5 days, and paclitaxel (175 mg/m^2) daily, as a 3-hour infusion, every 21 days. According to final results there were no statistically significant differences between the two agents (Gordon A, etal, ASCO98, Abs. 1374:356a).

A new indication for topotecan monotherapy is small-cell lung cancer (sclc). Several phase III clinical trials have been undertaken by the International Topotecan Study Group for this indication. An international multicenter 211-patient randomized phase III clinical trial compared topotecan (1.5 mg/m^2), administered on days 1-5, every 21 days, with a CAV regimen consisting of cyclophosphamide (1000 mg/m^2), doxorubicin (45 mg/m^2) and vincristine (2 mg), all administered on day 1, every 21 days, in patients with recurrent sclc whose disease had not progressed within 60 days of cessation of first-line therapy. The overall response rate was 26/107 (24.3%) in the topotecan arm and 18/104 (17.3%) in the CAV arm. MST was similar in both groups, 5.8 months with topotecan compared to 5.7 months with CAV, and time to progression was 3.1 months and 2.8 months, respectively. Grade 4 neutropenia occurred in 69% of topotecan-treated patients (38% courses) versus 73% in CAV-treated patients (51% courses) but Grade 4 thrombocytopenia was rarer, occurring in 29%/10% versus 5%/1.5%, respectively (Schiller J, etal, ASCO98, Abs. 1755:456a). An NDA was filed for treatment of sensitive sclc based on results of this trial and, in June 1998, FDA's Oncologic Drugs Advisory Committee (ODAC) recommended approval of Hycamtin for second-line treatment of sensitive sclc based on this trial and on three open label, non-comparative trials involving 319 patients with sclc that recurred or progressed after treatment with first-line chemotherapy.

Topotecan is being investigated alone or in combination with other chemotherapeutics in treating a variety of advanced solid tumors:

- as both second- and first-line therapy in advanced sclc in combination with cyclophosphamide, ifosfamide, etoposide, or a platinum-based drug
- as second-line therapy with etoposide in advanced ovarian cancer or first-line monotherapy or in combination with cispaltin and paclitaxel, in newly-diagnosed Stage III/IV ovarian cancer
- as second-line monotherapy or in combination with a platinum-based drug in refractory acute leukemia
- as first- and second-line treatment of myelodysplastic syndrome (MDS)
- as second-line monotherapy for advanced non Hodgkin's lymphoma (low-grade and intermediate-grade)
- in various sequential and/or high-dose, multicycle chemotherapy regimens in combination with hematopoietic factors in advanced disease
- as first-line monotherapy in pediatric malignancies

An oral formulation of topotecan is also being evaluated with promising results to date from an ongoing phase III randomized, multicenter clinical trial in which topotecan is administered either orally (2.3 mg/m^2) or IV (1.5 mg/m^2) on days 1-5, every 21 days, to patients with advanced epithelial ovarian carcinoma (FIGO III/IV) who had been treated with one platinum-based regimen. Among 270 randomized patients (IV=131 and PO=139) response rates were similar (21.5% IV versus 21.4% PO). Hematologic toxicities such as Grade 4 anemia (occurring in 2.8% of IV courses versus 1.4% of PO) and thrombocytopenia (12.8% versus 12.5%, respectively) were similar in both arms but Grade 4 neutropenia (57.4% versus 19.6%, respectively) was less frequent with the oral regimen (Gore M, etal, ASCO98, Abs. 1346:349a).

Inex Pharmaceuticals (Vancouver, BC, Canada), in collaboration with the University of Kentucky College of Pharmacy (Lexington, KY) and the British Columbia Cancer Agency (Vancouver, BC, Canada), has developed a procedure (TCS) to efficiently encapsulate topotecan within lipid-based carriers by employing an ion gradient loading technique. A liposomal formulation of topotecan may prevent the rapid systemic inactivation and elimination of the drug by maintaining therapeutic drug levels over a prolonged period of time. In contrast to earlier liposomal delivery studies in which camptothecins were inserted into the lipid bilayer, this technique entraps topotecan predominantly in the aqueous core of the carrier. In all treatment schedules in murine models, topotecan TCS exhibited much greater antitumor activity than the free drug (Madden TD, etal, ASCO98, Abs. 754:196a).

Irinotecan (CPT-11, Camptosar; Pharmacia & Upjohn), was approved in the USA in May 1996 and launched in June 1996, in as second-line treatment of advanced, refractory colorectal cancer, based on a single-arm, phase II clinical trial (see FO, p 542) that demonstrated tumor shrinkage. In April 1998, Pharmacia & Upjohn filed an NDA to obtain an unconditional approval of the drug based on phase III clinical trial results that show longer survival and improved QoL. In 1997, sales of Camptosar

were $153.8 million, up 165% from 1996 levels. Sales in the first quarter of 1998 were $42 milion, up 1% over 1997 levels. In 1997, the AWP of one cycle of irinotecan was $4,100-$6,150. Campto, the irinotecan formulation marketed by Rhône-Poulenc Rorer outside the USA, has been approved and/or launched in over 20 countries. CPT-11 has also been on the market in Japan since 1994, for primary, lung, cervical and ovarian cancer.

Irinotecan will probably evolve into standard therapy after 5-FU failure and refute the notion that the only alternative for patients who failed 5-FU is palliative best supportive care (BSC) without additional chemotherapy. In a phase III multicenter randomized clinical trial of CPT-11 versus BSC alone, in 5-FU-resistant metastatic colorectal cancer that progressed within 6 months of treatment, 279 patients were randomly assigned in a 2:1 ratio (189 on CPT-11 and 90 on BSC) to either CPT-11, (350 mg/m^2 or 300 mg/m^2 if age ≥70 or performance status=2), every 3 weeks, plus optimal BSC, or optimal BSC alone. Within a median follow-up of 13 months, overall survival was 2.6 times greater in the CPT-11 group, 36.2% versus 13.8%, respectively. This survival benefit, remained highly significant even when adjusted for prognostic factors. Survival without deterioration of performance status or weight loss >5%, and pain-free survival, were significantly improved in the CPT-11 group. In the QoL analysis, all scores that were significantly different, except diarrhea, were in favor of CPT-11 and time to QoL deterioration was significantly longer with CPT-11 (Cunningham D, etal, ASCO98, Abs. 1:1a).

In another multicenter phase III clinical trial, 267 patients were randomized to CPT-11 (300-350 mg/m^2), every 3 weeks, or one of the following 5-FU-based regimens:

- daily IV bolus 5-FU (400 mg/m^2) + daily continuous IV infusion of 5-FU (600 mg/m^2) + folinic acid on days 1-2, every two weeks
- daily continuous IV infusion of 5-FU (250-300 mg/m^2) until toxicity
- daily 24-hour IV infusion of 5-FU (2.6-3g/m^2) ± folinic acid, weekly, for 6 weeks with 2 weeks rest

All in all, 256 out of 267 enrolled patients were treated, 127 with CPT-11 and 129 with any of the 5-FU regimens. Within a median follow-up of 15 months, overall survival was significantly higher in the CPT-11 group, with the one-year survival being 1.4 times greater (44.8% versus 32.4%, respectively). Progression-free survival was also significantly improved in the CPT-11 group with a median of 4.2 months versus 2.9 months. Therefore, treatment with CPT-11 resulted in a significantly improved survival compared to infusional 5-FU, with a comparable QoL (Van Cutsem E, ASCO98, Abs. 984:256a).

Irinotecan is being currently evaluated for treatment of various advanced solid tumors:

- both as second- and first-line therapy in advanced small and non-small cell lung cancer (sclc and nsclc) in combination with taxanes, platinum agents or gemcitabine
- as first- and second- line monotherapy and in combination with 5-FU, in advanced colorectal cancer
- as first-line monotherapy in advanced hepatocellular cancer
- as second-line therapy in recurrent/progressing malignant glioma
- as second-line monotherapy or in combination with cisplatin in recurrent/progressing cervical cancer

In order to reduce systemic toxicity, mostly manifesting as severe diarrhea and myelosuppression, irinotecan regimens involve continuous infusions, some lasting as long as 96 hours, which complicates therapy and may limit the drug's utility. Researchers using a rat model mimicking irinotecan's clinically observed toxicity profile, found that intraperitoneal administration of interleukin 15 (IL-15), supplied by Immunex (Seattle, WA), provided complete protection against a lethal dose of CPT-11, without affecting its antitumor activity and dramatically protected against irinotecan-induced toxicity in the duodenum (Rustum YM, etal, ASCO98. Abs. 753:196a).

Other topoisomerase I inhibitors are being synthesized with greater water solubility that also exhibit increased antitumor activity and reduced toxicity.

9-aminocamptothecin (9-AC), under development by IDEC Pharmaceuticals (San Diego, CA), is being investigated in phase I/II clinical trials which were initiated in November 1997, involving patients with any of eight types of solid tumors, such as nsclc, or colorectal, pancreatic, gastric, bladder, prostate, head and neck, or kidney cancer.

9-nitrocamptothecin (9NC) or RFS 2000, another lipid soluble camptothecin analog is in development by SuperGen (San Ramon, CA), in collaboration with the Stehlin Foundation for Cancer Research (Houston, TX). A phase II clinical trial in advanced, biopsy-proven, pancreatic carcinoma enrolled 53 patients (64% with metastatic disease and 42% previously-treated patients, mostly with 5-FU and gemcitabine) between March 1995 and August 1997, who completed at least two courses of therapy, each consisting of oral 9NC (1-1.5 mg/m^2), daily, for five consecutive days, followed by 2 days rest, repeated four times. There were no treatment-related deaths. Observed toxicities were Grade 3/4 leukopenia (13%), anemia (23%), thrombocytopenia (4%), cystitis (2%), diarrhea (4%), and nausea (2%) that were rapidly reversible after discontinuing treatment. Among evaluable patients, 32% were responders, 32% were stable, and 26% were non-responders; 10% were not yet evaluable. MST was 9.1 months (responders), 8.8 months (stable), and 5.9 months (non-responders), with 53% still surviving as of November 1997 (Stehlin, JS Jr, etal, ASCO98, Abs. 1012:263a). The drug is also being investigated in phase II clinical trials in ovarian cancer and may be effective in prostate cancer and leukemia.

DX-8951f, a water soluble derivative of camptothecin, is under development by Daiichi Pharmaceutical (Fort Lee, NJ). Against malignant cell lines and human tumor xenografts, its antitumor activity was greater than that of topotecan and it was not MDR-modulated. In an ongoing phase I clinical trial at M. D. Anderson Cancer Center, DX-8951f was administered as a 24-hour infusion, every 3 weeks, at a starting daily dose of 0.15 mg/m^2 to 8 patients, 7 with metastatic colon cancer and 1 with lung cancer, who had been treated with prior chemotherapy. Dose escalation is continuing in order to define MTD (Royce M, etal, ASCO98, Abs. 757:197a).

Karenitecins BNP 1100 and 1350 are novel orally-active highly lipophilic semi-synthetic derivatives of camptothecin, under development by BioNumerik Pharmaceuticals (San Antonio, TX). The potency of karenitecins that is significantly higher than existing analogs of camptothecin, is attributable to increased lactone stability, greater lipophilicity and novel modifications. Karenitecins were engineered for superior oral bioavailability, insensitivity to various sources of drug resistance, and avoidance of certain untoward drug metabolism reactions. Karenitecins are active *in vitro* against a wide range of human cancer cell lines and exhibit substantial antitumor activity against subcutaneously established human xenografts including prostate, breast, and colon cancer and nsclc (Hausheer F, etal, AACR98, Abs. 2862:420-21). In *in vitro* tests, a sequential combination protocol using clinically feasible doses and schedules of the thymidylate synthase (TS) inhibitor ZD1694 (Tomudex; Zeneca) and karenitecin BNP 1100 and 1350, induced a near 100% net cell-killing effect on various tumor cell lines (Matsui S, etal, AACR98, Abs. 783:203a). BNP 1350 is in late preclinical development with phase I clinical trials being planned.

Lurtotecan (GI147211C or GW211), a novel water soluble camptothecin analog, under developmement by Glaxo Wellcome, is in phase II clinical trials in various malignancies, including ovarian and breast cancer and sclc. Main toxicities reported in a phase I clinical trial were hematologic and gastrointestinal. Among 46 evaluable patients with relapsed ovarian cancer, enrolled in a phase II clinical trial of GW211 (1.2 mg/m^2), administered daily for 5 days, every 3 weeks, there was 1 (2.2%) CR, 7 (15.2%) PR and disease stabilized in 19 (41.3%) and progressed in 19 (V. Oosterom AT, etal, ASCO97, Abs. 1250:349a). In a phase II clinical trial being conducted by the EORTC Early Clinical Studies Group (ECSG), GW211, administered daily, for 5 days, every 3 weeks, was used as salvage treatment for refractory or relapsing sclc patients who were stratified by "response to prior treatment" with S1 defined as refractory (non responders or relapsing within 3 months after prior chemotherapy) and S2 as potentially sensitive (relapsing later than 3 months). A total of 62 eligible patients were entered (S1=25, S2=37) of whom 19 S1 and 28 S2 were evaluable for response. Hematologic toxicities were neutropenia (Grade 3/4 in 23% of cycles) and thrombocytopenia (Grade 3/4 in 26%); neutropenic fever occurred in 4 patients. The main non-hematologic toxicities were asthenia and nausea, mostly Grade 2, reported in 50% of patients. There were 4/19 (21%) PR in the S1 group and 6/28 (21%) in the S2 group (Wanders J, ASCO98, Abs. 1823:474a).

A unilamellar liposomal formulation of Lurtotecan, NX-11, is being developed in collaboration with NeXstar Pharmaceuticals (Boulder, CO). It was shown in animal models that formulating Lurtotecan in low clearance liposomes, improves antitumor activity by increasing drug exposure and, possibly, by enhancing drug delivery to resistant tumors (Emerson DL, etal, AACR98, Abs. 1897:278).

TAS-103, a novel dual topo I and II inhibitor, is being evaluated by Taiho Pharmaceutical (Tokyo, Japan). As of early 1998, 22 patients with advanced refractory solid tumors had been entered in a phase I clinical trial, being conducted at Johns Hopkins Oncology Center (Baltimore, MD). The principal drug toxicity has been myelosuppression. Nonhematologic toxicities have been mild. No responses were observed but disease stabilized in patients with colon, head and neck, and renal cancer, and nsclc, for 5, 6, 4, and 5 months, respectively. MTD and phase II dose appears to be between 280-350 mg/m^2 (Donehower R, etal, ASCO98, Abs. 806:209a).

XR 5000, another dual topo I and topo II inhibitor under development by Xenova (Slough, UK), is in phase I clinical trials as a 120-hour infusion; a 3-hour infusion protocol was abandoned in August 1997 because of adverse reactions.

Taxanes

The market for taxanes continues to expand as new indications are approved and the drugs are being used in numerous combination regimens. Global combined sales of taxanes were $1,188 million in 1997.

Paclitaxel

Taxol continues to perform for Bristol-Myers Squibb, bringing in $940 million in revenues worldwide in 1997, with 65.3% generated in the USA. In the first quarter of 1998, worldwide sales were $251 million, up 15% from the comparable 1997 period, with USA sales pegged at $162 million, up 14%, and foreign sales at $89 million, up 27%. Industry sources expect Taxol sales to exceed $1.1 billion in 1998 and reach $1.4 billion by 2000.

In April 1998, the FDA approved paclitaxel as first-line or subsequent therapy, in combination with cisplatin, for advanced ovarian cancer (see FO, p 571), after a recommendation by ODAC in March 1998. Approval of this regimen was based on longer time to disease progression (16.6 months versus 13 months) and MST (35.5 months versus 24.2 months). Response was 62% with the paclitaxel/cisplatin combination compared to 48% for cyclophosphamide/cisplatin. Adverse events, primarily neutropenia, occurred in 81% of patients treated with the paclitaxel-based combination compared to 58% in the cyclophosphamide/cisplatin group. The recommended regimen is

Exhibit 6
Combination/Multimodality Therapies in Prostate Cancer

Agent ❑ Combination Regimen	Phase ❑ Indication (# enrolled)	Results	Site ❑ Reference
Estramustine (140 mg) PO *tid* on days 1-7 + docetaxel (70 mg/m^2) 1-hour IV infusion on day 1	Phase II ❑ refractory prostate cancer (n=5)	4/5 (80%) PR lasting 2 months, 3+ months, 5+ months and 5+ months; 1/5 (20%) SD lasting 3+ months	Institute for Prostate Cancer Research and the Daniel Freeman Marina Hospital (Marina del Rey, CA) ❑ Scholz M, etal, ASCO98, Abs. 1319: 342a
Estramustine + vinblastine for 24 weeks over last 8 weeks of radiation therapy (3D-radiation therapy with total dose of 75.6 cGy)	Pilot ❑ localized prostate cancer (n=23)	9/23 too early to evaluate, 3/23 removed from study, 12/23 completed therapy	Memorial Sloan-Kettering Cancer Center (New York, NY) ❑ Curley T, etal, ASCO98, Abs. 1208: 314a
Estramustine (10 mg/kg) + carboplatin (6 AUC-every 4 weeks) + paclitaxel (60 mg/m^2 for level I and II; 80 mg/m^2 for level III, and 100 mg/m^2 for level IV)	Phase II ❑ advanced prostate cancer [n=15; 6 androgen-dependent (AD) and 9 androgen-independent (AI)]	3/5 (60%) AI experienced a >50% decline in PSA	Memorial Sloan-Kettering Cancer Center (New York, NY) ❑ Kelly WK, etal, ASCO98, Abs. 1249: 324a
Estramustine (280 mg) PO *tid* on days 1-5 + docetaxel (70 mg/m^2) on day 2 + dexamethasone (20 mg) PO *q* 6 hours x 3 doses on day 2, *q* 3 weeks versus dexamethasone monotherapy	AI prostate cancer (n=12 chemotherapy-naive)	No PSA declines of ≥50% were observed with dexamethasone alone; of those treated with the combination therapy, 7/8 (88%) experienced PSA declines of ≥50% and 5/8 (63%) PSA declines of ≥75%	Columbia-Presbyterian Medical Center (New York, NY) ❑ Shelton G, etal, ASCO98, Abs. 1324: 343a
Estramustine (14 mg/kg) PO, daily, for 21 days + docetaxel (40, 60, or 80 mg/m^2) *q* 21 days (MDT was 70 mg/m^2)	Phase I ❑ hormone refractory prostate cancer (n=17)	5/6 (83.3%) experienced mean PSA decline of 87%±12%	North Shore University Hospital, NYU Medical College (Manhasset, NY) ❑ Kreis W, etal, ASCO98, Abs. 1294: 335a
Estramustine (420 mg) PO *tid* on days 1-4 + docetaxel (35-40 mg/m^2) or vinorelbine on day 3, weekly x 4, *q* 6 weeks (regimen A); estramustine *tid* on days 1-3 (420 mg first 4 doses, 280 mg last 5 doses) + dexamethasone (4 mg) *bid* on days 1-3 + docetaxel on day 2, weekly x 2, *q* 3 weeks (regimen B)	Phase I/II ❑ metastatic hormone-refractory prostate cancer (n=24)	16/24 (66.7%) experienced PSA decline of ≥50%; 8/24 (33.3%) ≥75%	Cedars-Sinai Comprehensive Cancer Center (Los Angeles, CA) ❑ Natale RB, etal, ASCO98, Abs. 1302: 338a
Estramustine (560 mg) divided into 2 daily doses + etoposide (100 mg) once a day, PO, for a 14-day cycle, repeated *q* 28 days	Phase II ❑ hormone-refractory prostate adenocarcinoma (n=45)	1/14 (7%) CR, 7/14 (50%) PR	Oncologia LUGO (Italy) ❑ Cruciani G, etal, ASCO98, Abs.1268: 329a
Estramustine (600 mg/m^2) PO for 6 weeks + paclitaxel (118 mg/m^2) as a 3-hour weekly IV infusion x 6, *q* 8 weeks	Phase I ❑ metastatic hormone-refractory prostate cancer (n=12)	3/6 (50%) PR lasting 3 months, 3+ months and 6+ months	Fox Chase Cancer Center (Philadelphia, PA) ❑ Garay C, etal, ASCO98, Abs. 1278: 331a
Estramustine (8 mg/kg) PO in 3 divided doses on day 1, increased to 10 mg/kg on day 15 + strontium-89 (4 mCi) IV on day 7, repeated at 3 and 6 months	Phase II ❑ hormone-refractory prostate cancer (n=35)	9/29 (31%) experienced a PSA response (50% decline in ≥4 weeks)	Georgetown University (Washington, DC) ❑ Dahut W, etal, ASCO98, Abs. 1269: 329a
Estramustine (600 mg/m^2), daily, in weeks 1-4 and 6-10 + vinblastine (4 mg/m^2), weekly, in weeks 1-4 and 6-10 + strontium-89 (2.2 MBq/kg) *q* 12 weeks of a 12-week cycle	Phase II ❑ hormone-refractory prostate cancer (n=42)	17/32 (53%) experienced a PSA response (50% decline lasting 6 weeks); overall survival was13.8 months	Brown University Oncology Group (Providence, RI) ❑ Wehbe T, etal, ASCO98, Abs. 1341: 348a
Mitoxantrone (21 mg/m^2) IV *q* 3 weeks for 7 cycles for patients with no previous pelvic irradiation (arm I); mitoxantrone (17 mg/m^2) IV *q* 3 weeks for 8 cycles for those with previous pelvic irradiation (arm II) + hydrocortisone (40 mg) + GM-CSF (500 mg) daily, starting at day 3, and continuing until ANC ≥1500/nm^3 after day 12	Phase II ❑ hormone-refractory prostate cancer (n=28)	Arm I: 2/10 (20%) PR; arm II: 2/12 (17%) PR (PSA-based responses)	Cancer and Leukemia Group B (Chicago, IL) ❑ Levine EG, etal, ASCO98, Abs. 1297: 336a
Mitoxantrone (12 mg/m^2) pulse administration + paclitaxel (175 mg/m^2) as a 3-hour infusion, *q* 3 weeks, for a maximum of 9 courses	Phase II ❑ hormone-refractory prostate cancer (n=17)	Median duration of response was 5.1 months (range=2-13+ months)	Moffitt Cancer Center and University of South Florida (Tampa, FL) ❑ DeConti R, etal, ASCO98, Abs. 1270: 329a

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Mitoxantrone (10, 12, 14, 16 mg/m^2) IV, *q* 3 weeks, beginning on day 22 + strontium-89 (4 mCi) IV *q* 12 weeks + hydrocortisone (40 mg) PO, daily	Phase I/II ❑ hormone-refractory prostate cancer (n=10)	3/8 PSA declined 81%, 87%, 94%; there were 2 SD; 100% pain relief (chronic thrombocytopenia may be the DLT)	Washington University (St. Louis, MO) and University of Chicago ❑ Cohn H, etal, ASCO98, Abs. 1265: 328a
5-FU (1000 mg/m^2) daily, for 5 days, *q* 3 weeks + mitomycin C (10 mg/m^2) IV, *q* 6 weeks	Phase II ❑ progressive hormone refractory prostate cancer (n=44)	13% CR, 25% PR, 38% SD; MST was 6 months (range= 0-33 months)	Sheba Medical Center (Tel Hashomer, Israel) ❑ Tichler T, etal, ASCO98, Abs. 1331: 345a
Goserelin (3.6 mg) *q* 4 weeks + flutamide (250 mg) *tid,* for 2 months before and during radiation therapy (arm I) versus radiation therapy alone (arm II)	Phase III ❑ locally advanced (Stage T2-T4) prostate cancer (n=471)	72% survived 5 years and 51% 8 years in arm I versus 68% and 43%, respectively, in arm II	Multicenter ❑ Pilepith MV, etal, ASCO98, Abs. 1185:308a

135 mg/m^2 of paclitaxel, followed by 75 mg/m^2 of cisplatin, administered every 24 hours, once every three weeks. In March 1998, ODAC also recommended a similar combination regimen as first-line chemotherapy for a limited subpopulation with nsclc.

It appears, however, that anthracyclines remain the therapy of choice in advanced breast cancer. In a multicenter clinical trial at EORTC-IDBBC/ECSG participating centers, 331 women with advanced breast cancer who may have been pretreated with adjuvant chemotherapy without anthracyclines or taxanes, were randomized either to paclitaxel (200 mg/m^2), administered over 3 hours (n=166), or doxorubicin (75 mg/m^2) (n=165), every 3 weeks. The protocol involved delivery of 7 courses unless there was disease progression (PD) that triggered an early crossover to the alternative drug, or unacceptable toxicity. Objective response in first-line was significantly better for doxorubicin (6% CR, 35% PR, 36% SD, 13% PD, 10% NE) than for paclitaxel (2% CR, 23% PR, 35% SD, 31% PD, 9% NE), with a longer median progression-free survival (7.5 months for doxorubicin versus 4.2 months for paclitaxel). Second-line, cross-over treatment with doxorubicin (n=87) resulted in 29% PR, 49% SD, 15% PD and 7% NE, whereas cross-over to paclitaxel (n=74) resulted 14% PR, 39% SD, 43% PD, 4% NE. Differences in MST (1.51 years for doxorubicin versus 1.28 years for paclitaxel), were not significant but the toxicity profile was. Grade 3/4 mucositis, GI side-effects, cardiotoxicity and febrile neutropenia were more frequently observed on doxorubicin but more instances of myalgia and neurotoxicity were associated with paclitaxel. QoL analysis showed more burden from side-effects but less bone pain and better pain control with doxorubicin. Because, overall, there were no major differences in global burden of disease and treatment, in monotherapy, doxorubicin followed by paclitaxel is the regimen of choice. However, because these two drugs are not totally cross-resistant, alternating regimens or combinations deserve consideration (Gamucci T, etal, ASCO98, Abs. 428:111a).

Numerous other paclitaxel combinations are being evaluated in clinical trials (see FO, pp 635-641):

- in combination with a platinum-based agent and either etoposide or vinorelbine, or with oral etoposide in advanced nsclc
- as part of a multimodality therapy in glioblastoma multiforme
- in combination with mitoxantrone or a platinum-based agent and epirubicin, as first-line chemotherapy in advanced breast cancer
- as a radiosensitizer in metastatic/recurrent cervical cancer and, alone or in combination with a platinum-based agent, in advanced squamous cell carcinoma of the head and neck
- in combination with ifosfamide and cisplatin as salvage therapy in pretreated advanced ovarian cancer
- as neoadjuvant treatment in esophageal cancer
- in combination with 5-FU and leucovorin as first-line treatment of metastatic breast cancer
- in various high-dose chemotherapy regimens
- in combination with a platinum-based agent in metastatic locoregional nasopharyngeal cancer

Despite loss of market exclusivity for Taxol in December 1997, Bristol-Myers Squibb continued to prevail over its competition. In April 1997, the District Court in Utrecht revoked Yew Tree Pharmaceuticals' (Haarlem, The Netherlands) marketing approval for Yewtaxan, its generic paclitaxel, in the Netherlands, after BMS filed suit claiming that the filing lacked sufficient clinical data. It is expected that Yew Tree will appeal the decision to support its filing under the European Community's mutual recognition procedure which is currently in review. However, as it stands today it appears that Taxol's exclusivity in Europe will be extended to 2003.

Similarly, BMS has to date successfully protected its USA market. Potential direct competition to Taxol is expected from Immunex and IVX BioScience (was IVAX; Miami, FL) that have each filed ANDAs requesting FDA approval of their generic paclitaxel formulations. In addition, IVX, through its wholly-owned subsidiary, Baker Norton Pharmaceuticals, obtained a tentative FDA approval in December 1997 for Paxene, its branded formulation of paclitaxel, for the treatment of Kaposi's sarcoma (KS). However, because of Taxol's patents and orphan drug status for KS, IVX is not allowed to initiate marketing of this drug in the USA until after 2004. Both Immunex and IVX

have certified, in their ANDA applications, that certain use patents held by BMS relating to Taxol are invalid or not infringed by their products. BMS has challenged this certification, filing lawsuits for infringement of its patents. IVX has filed a counter claim against BMS to invalidate the patents, and has also asserted claims against BMS for violations of Federal anti-trust laws and unfair competition. IVX is also contesting Taxol's orphan drug status in KS, claiming that Paxene is a different entity than Taxol and is more effective with fewer side effects.

In June 1998, IVX agreed to acquire the Immunex ANDA, the first ANDA filed with the FDA for paclitaxel, in exchange for an unspecified cash payment. Subject to a favorable outcome of patent litigation, the Immunex ANDA will likely be entitled to six months of exclusivity from other generic competition. IVX also agreed to acquire from Immunex inventories of bulk paclitaxel and direct the defense of its own and the Immunex lawsuits, with Immunex reimbursing IVX for a percentage of its patent litigation expenses. If the Immunex ANDA is approved, IVX will pay Immunex royalties based on net sales of generic paclitaxel. In addition, Immunex will help IVX promote generic paclitaxel using its oncology sales force, earning additional fees for this effort. This agreement does not affect Immunex' paclitaxel marketing activities outside the USA. Boehringer Ingelheim Canada (Burlington, Ontario), Immunex' marketing partner in Canada, began marketing generic paclitaxel in Canada in the fall of 1997.

In a separate agreement, IVX has appointed Immunex to promote Paxene when it receives final FDA approval to enter the USA market. Immunex will earn fees based on all Paxene sales in the USA during the period in which it promotes Paxene. This transaction is subject to Federal Trade Commission review under the Hart-Scott-Rodino Act.

Before entering into the agreement with Immunex, IVX terminated its marketing collaboration with NaPro BioTherapeutics (Boulder, CO) but retained a supply agreement and obtained a royalty-free non-exclusive license in the USA, Europe and certain other markets, to NaPro's pending patents for a stable formulation of paclitaxel. In exchange, IVX paid $8.1 million and will pay an additional $6.4 million upon issuance of the patents. It is anticipated that Hauser (Boulder, CO), Immunex' current supplier of paclitaxel, will supply IVX as well, but negotiations have not been finalized to date.

Mylan Pharmaceuticals (Morgantown, WV), another developer of generic paclitaxel, also filed suit in 1998 to invalidate BMS' use patents. The company claims that the use patents are not valid because of pre-existing published data regarding infusion methods for paclitaxel (McGuire W, etal, Annals of Internal Medicine 1989, 111(4):273-279) and that BMS is violating antitrust laws.

In 1997, in the USA, the AWP of one cycle of Taxol was $1,950-$2,700, costing between $6,825-$9,450 for an average regimen involving 3.5 cycles. Costs are similar or higher in overseas markets. The high cost of paclitaxel, a drug currently considered state-of-the-art treatment for several deadly cancers such as advanced ovarian cancer, is becoming a global health and political issue. In June 1998, Boehringer Ingelheim reduced the cost of a 30 mg 5 ml vial of it generic paclitaxel from CDN$130 to CDN$99. This price is almost half of Taxol's listed Canadian price and illustrates the vulnerability of Bristol-Myers Squibb's Taxol franchise to generic competition. In 1997, the cost of Taxol to the Canadian healthcare system was CDN $18 million. The high price of Taxol is restraining its use by some centrally-funded healthcare systems. For instance, in Britain, where paclitaxel is rarely used, oncologists and patient advocacy groups are demanding that the UK health system reimburse for the drug for all who need it.

Docetaxel

As of early 1998, docetaxel (Taxotere; Rhône-Poulenc Rorer) had been approved in 56 countries for various indications, but primarily as second-line treatment of advanced breast cancer. In 1997, the AWP of one cycle of Taxotere was $3,350-$4,400. Worldwide sales of Taxotere grew by 198% in 1997 to reach $248 million but were only $52 million in the first quarter of 1998. It appears that the drug is still struggling to compete against Taxol in the USA.

In June 1998, the FDA approved Taxotere for expanded use for the treatment of refractory, locally-advanced or metastatic breast cancer, based on results from large, international phase III trials. Taxotere had received a conditional FDA approval for this indication in May 1996 that required that the company complete two additional phase III clinical trials in metastatic breast cancer. Taxotere was previously approved for treatment of locally-advanced or metastatic breast cancer which progressed during anthracycline-based therapy, or relapsed during anthracycline-based adjuvant therapy.

In one randomized phase III multicenter clinical trial that compared Taxotere (100 mg/m^2) delivered by a one-hour infusion, every 3 weeks, to mitomycin C (12 mg/m^2), administered every 6 weeks, in combination with vinblastine (6 mg/m^2) every 3 weeks, in patients with refractory metastatic breast cancer, the one-year survival rate was 49% with Taxotere, compared to 33% with the combination; the 18-month survival rate was 33% and 21%, respectively (Nabholtz JM, etal, ASCO98, Abs. 519:148a). In another randomized phase III clinical trial, comparing Taxotere to doxorubicin in refractory metastatic breast cancer, overall response rate in patients treated with Taxotere was 46% versus 32% for doxorubicin; response was 58% versus 44%, respectively, as first-line treatment. Among patients whose disease had progressed on previous regimens containing alkylating agents, and in those with liver metastases, the response rate was significantly higher with docetaxel than doxorubicin, 47% versus 24% in resistant disease, and 54% versus 27% in patients with liver metastases. In patients with normal liver function, side effects reported to date include neutropenia, thrombocytopenia, anemia, fluid retention, hypersensitivity, nausea and diarrhea. A premedication regimen with corticosteroids

Exhibit 7
Trends in Oncology

Observation	Comments
Death rates attributable to cancer have been declining	Several courses of chemotherapy, using first-, second-, and third-line regimens, as well as experimental protocols, have extended patient's lives so that, currently, more and more people survive with active disease; this may prove to have a short-lived benefit in survival rates unless more effective drugs become available
Many pharmaceutical and biotechnology firms are actively pursuing research in this area	The incredible success of Bristol-Myers Squibb's Taxol drove the point that oncology can harbor blockbuster drugs; also, the oncology drug market, encompassing not only anticancer agents, but such products as analgesics, antiemetics, anti-infectives and hematopoietic factors, among others, as well as diagnostics and devices, is becoming one of the most dynamic healthcare sectors
Numerous new drugs are being introduced	FDA's willingness to accept tumor response as an endpoint requirement and to expedite approval of certain drugs, has resulted in an unprecedented influx of new anticancer drugs offering, in many cases, the first alternative standard therapy in decades
Basic science, particularly molecular biology, is generating an incredible wealth of leads regarding mechanisms of malignancy	Numerous novel agents are in development based on never-before studied approaches; drugs regulating processes leading to or promoting malignancy rather than indiscriminate cell killing, are creating treatments with high selectivity and fewer side effects
Better understanding of the action of current therapeutics is creating more effective treatment options	New combination therapies take advantage of complimentary action of certain chemotherapeutics and /or regulatory agents, with a goal to also prevent/reverse drug resistance
Better management of complications	Effective management of complications has enabled delivery of higher doses of cytotoxic agents, resulting in higher responses but such regimens have not extended survival
A choice of various chemotherapeutics is becoming available for cancers of similar type and stage	For the first time in decades multiple chemotherapy treatment options have been introduced for several major cancers
Transformation of cancer from a short-term, almost acute condition, to a long-term manageable disease	It may be necessary that cancer patients who survive after the initial multimodality approach intended to resect/kill the bulk of existing malignancy, are then treated on a chronic basis with regulatory agents to check micrometastases and prevent recurrence
Exhaustive profiling of tumors down to the molecular level	Molecular diagnostics promise to provide a highly sensitive means of assessing treatment effectiveness
Individualized treatment	Genomics promises to copiously profile each individual's tumors, based on a variety of markers, to customize therapy

is recommended in order to prevent or reduce hypersensitivity and fluid retention. A National Surgical Adjuvant Breast and Bowel Project (NSABP) trial for node-positive breast cancer, using docetaxel in combination with standard therapy, is currently recruiting new patients. Also, a clinical trial comparing docetaxel to paclitaxel in the treatment of advanced breast cancer, is ongoing.

Docetaxel, like paclitaxel is being investigated alone or in combination with other chemotherapeutics in numerous indications, among them:

- as monotherapy, or in combination with epirubicin or doxorubicin, as first-line treatment for advanced breast cancer
- in combination with a platinum-based agent or gemcitabine, or 5-FU, or vinorelbine, or mitoxantrone, as second-line treatment for advanced breast cancer
- in the neoadjuvant setting, in combination with doxorubicin, in operable Stage II breast cancer
- concurrently with radiation therapy in Stage III unresectable nsclc and as monotherapy or in combination with gemcitabine or irinotecan, or a platinum-based agent, as first-line therapy in advanced/metastatic nsclc
- as first-line monotherapy in sclc
- as monotherapy or in combination with a platinum-based agent with or without 5-FU and leucovorin, as first-line treatment for advanced squamous cell carcinoma of the head and neck
- in combination with a platinum-based agent and epirubicin or cyclophosphamide, in advanced ovarian cancer
- in combination with a platinum-based agent in metastatic urothelial cancer
- as monotherapy or in combination with estramustine in hormone-refractory prostate cancer
- as salvage monotherapy in advanced gastric cancer
- as first-line monotherapy in pancreatic cancer
- as monotherapy in anthracycline-refractory advanced soft tissue sarcoma
- as monotherapy for second-line treatment for advanced Kaposi's sarcoma

Other taxanes/taxoids in development have been described in various previous FO articles (see FO, pp 638-641).

RPR-109881A, a novel, highly potent taxane analog, under development by Rhône-Poulenc Rorer, is being investigated in ongoing phase I clinical trials, in various regimens (Vernillet L, ASCO98, Abs. 749:194a; Slaughter M, etal, ASCO98, Abs. 748:194a; and Eisenhauer E, etal, Abs. 746:194a).

EnzyMed (Iowa City, IO) a private company, in collaboration with the University of Iowa (Iowa City, IO), has synthesized a formulation of paclitaxel that is 1,600-fold more water-soluble than the current commercially available versions (Khmenitsky YL, etal, J Am Chem Soc, 26 Nov 1997, 119(47):11554-11555). EnzyMed specializes in the discovery, optimization, and screening of pharmaceutical and agrichemical compounds using combinatorial biocatalysis, a technology that integrates iterative enzymatic and microbial reactions with selected chemical synthesis to create diverse new compounds. EnzyMed's technology is applicable to small molecules, natural products, and complex synthetic leads.

Other Chemotherapeutics

Mitoxantrone (Novantrone; Immunex), approved for treatment of acute myelogenous leukemia (AML) and, recently, also for hormone-refractory prostate cancer, rung up sales of $51.6 million in 1997; first quarter 1998 sales were $13.4 million. The drug is being evaluated in many settings, primarily in hematologic malignancies, but also as first-line treatment of advanced breast cancer, in combination with paclitaxel, and in many high-dose chemotherapy regimens.

Gemcitabine (Gemzar; Eli Lilly) was approved in the USA for refractory nonresectable Stage II, III or IV adenocarcinoma of the pancreas in 1996 and, in March 1998, it was recommended for approval by ODAC as monotherapy, or in combination with cisplatin, in locally-advanced or metastatic Stage III/IV nsclc. Worldwide sales were $175 million in 1997, up 183% from 1996. Worldwide sales were $57 million in the first quarter of 1998, up 72% over 1996.

Numerous clinical trials, many combination phase I studies, are in progress evaluating gemcitabine in many types of solid tumors. Noteworthy among them:

- various combinations in advanced nsclc, including one with epirubicin that produced a CR + PR response of 50% (ASCO98, Abs. 1942:504a), and a combination with cisplatin that resulted in a higher response rate (31% versus 9.1%) and longer time to progression (6.8 months versus 4.2 months) than cisplatin monotherapy in chemotherapy-naive patients (Sandler A, etal, ASCO98, Abs. 1747:454a)
- as monotherapy or in combination with cisplatin for chemotherapy-naive advanced pancreatic cancer
- in combination with cisplatin for advanced mesothelioma, ovarian cancer, heavily pretreated breast cancer and head and neck cancer
- as monotherapy in platinum-refractory Mullerian (fallopian tube and primary peritoneal) cancer
- as monotherapy in refractory germ cell tumors

NEWLY APPROVED CHEMOTHERAPEUTICS AND ADJUNCT THERAPIES

The pace of approvals for chemotherapeutics has speeded up after the FDA relaxed some of its requirements both in NDA and supplemental NDA reviews.

Anzemet

Dolasetron (Anzemet; Hoechst Marion Roussel), a 5HT-3 antagonist, was approved in the USA in November 1997, and was launched in February 1998, for prevention of chemotherapy-induced emesis as well as the prevention and treatment of postoperative emesis. In the USA its AWP is $149.88 for a single-dose 100 mg vial and $330 for 5 tablets of 100 mg each. The drug has also been launched in several European markets.

Capecitabine

Capecitabine (Xeloda; Hoffmann-La Roche), is a novel 5-FU prodrug, an oral tumor-activated fluoropyrimidine carbamate anticancer agent, that is converted intracellularly to 5-FU by three enzymes acting in sequence. These enzymes exist in higher levels in cancer cells than in normal tissues, thus the drug is selectively activated mostly in tumor cells. The drug is targeting advanced stage breast and colorectal cancer and has shown higher response rates, improved time to disease progression, and fewer drug-related side effects, than standard therapy. In November 1997, Roche filed an NDA for accelerated approval in the USA as third-line therapy in locally-advanced or metastatic breast cancer that is refactory to anthracycline and/or paclitaxel-based chemotherapy and carries an extremely poor prognosis. The filing was based on a phase II clinical trial involving 163 patients at 25 centers in the USA and Canada, that showed an objective response rate of 20%, including three CR; MST was 13 months. In March 1998, ODAC recommended capecitabine and in June 1998, the FDA approved the drug for this indication but, as a condition of accelerated approval, Roche has agreed to continue clinical studies to establish outcomes.

Capecitabine is also being evaluated as second-line therapy in anthracycline-refractory breast cancer and in combination with taxanes. In a randomized phase II clinical trial, designed to evaluate the response rate in breast cancer patients who failed previous anthracycline therapy, conducted in Europe, capecitabine (2510 mg/m^2) was administered daily, in two separate doses, on days 1-14 or with paclitaxel (175 mg/m^2) on day 1, each every 3 weeks. This study was prematurely discontinued as many patients either wanted, or did not want, paclitaxel and refused to be

Exhibit 8
Worldwide Markets of Selected Chemotherapeutics Biologicals and Adjuncts

Developer ❑ Marketer ❑ Affiliate(s)	Drug Category	Generic Name ❑ Number ❑ Brand Name	Approved and Pending Indications	WW (USA) 1997 Sales ($ mil.)
Chemotherapeutics/Biologicals				
Barr Laboratories	Antiestrogen	Tamoxifen	Breast cancer	200.0
Berlex (Schering AG)	Purine analog	Fludarabine phosphate ❑ Fludara	Chronic lymphocytic leukemia (CLL)	78.3 (45.6)
Bristol-Myers Squibb	Taxane	Paclitaxel ❑ Taxol	Breast cancer, ovarian cancer	940.0 (614.0)
Bristol-Myers Squibb	Platinum-based agent	Paraplatin ❑ Platinol	Ovarian cancer and in various other combinations	437.0
Eli Lilly	Synthetic pyrimidine nucleoside	Gemcitabine ❑ Gemzar	Pancreatic cancer, lung cancer	175.0
Glaxo Wellcome	Semi-synthetic vinca alkaloid; norvinblastine derivative	Navelbine ❑ Vinorelbine	Nsclc	(60.6)
IDEC Pharmaceuticals ❑ Genentech (co-promote in the USA and Canada), Hoffmann-La Roche (outside the USA except Japan), Zenyaku Kogyo (Japan)	Monoclonal antibody	Rituximab ❑ IDEC-C2B8 ❑ Rituxan (USA), MabThera (Europe)	B cell non-Hodgkin's lymphoma (NHL)	5.5
Immunex	Synthetic anthracenedione	Mitoxantrone ❑ Novantrone	Acute myelogenous leukemia (AML), hormone-refractory prostate cancer	51.6
Immunex	Alkylating agent; lyophilized form of thiotepa, a nitrogen mustard derivative	Thiotepa ❑ Thioplex	Palliative for various cancers	22.4
Novartis ❑ Chugai Pharmaceutical (Japan)		Letrozole ❑ Femara	Second-line treatment in advanced breast cancer, in postmenopausal women with disease progression after antiestrogen therapy	
Rhône-Poulenc Rorer ❑ Chugai Pharmaceutical (Japan)	Taxane	Docetaxel ❑ Taxotere	Breast cancer and lung cancer	248.0
Schering-Plough	Non-steroidal antiandrogen	Flutamide ❑ Eulexin	Palliative in combination with an LHRH analog	214.0
Schering-Plough ❑ Biogen	Recombinant Interferon α-2b 2	Interferon α-2b ❑ Intron A	Advanced malignant melanoma and NHL	598.0[1]
Sequus Pharmaceuticals ❑ Schering-Plough	Liposomal anthracycline	Liposomal doxorubicin ❑ Doxil (USA), Caelyx (outside the USA)	Second-line treatment for AIDS-related Kaposi's sarcoma (KS)	(27.0)
SmithKline Beecham	Topoisomerase I inhibitor ❑ IV, PO	Topotecan ❑ Hycamtin	Ovarian cancer	85.0
TAP Pharmaceuticals ❑ Abbott Laboratories, Takeda	Formulation of leuprolide acetate, a synthetic non-apeptide analog of naturally occurring gonadotropin releasing hormone	Leuprolide acetate ❑ Lupron	Prostate cancer	990.0 (712.0)
Zeneca/UroCor	Synthetic decapeptide analog of luteininzing hormone-releasing hormone (LHRH)	Goserelin acetate ❑ Zoladex	Palliative in advanced breast and prostate cancer; also for management of endometriosis and endometrial ablation	578.0
Zeneca	Non-steroidal anti-estrogen	Tamoxifen ❑ Nolvadex	Adjuvant treatment of breast cancer	500.0
Zeneca/UroCor	Non-steroidal anti-androgen	Casodex	Palliative in combination with an LHRH analog	202.0
Zeneca	Aromatase inhibitor ❑ PO	Anastrozole ❑ Arimidex	Advanced breast cancer, in postmenopausal women with disease progression after antiestrogen therapy	85.0

— *continued on next page*

Adjunct Treatments				
Amgen	Recombinant erythropoietin; a glycoprotein that stimulates red blood cell production	Erythropoietin α (EPO) ❑ Epogen, Espo (Japan)	Chemotherapy-induced anemia	1,160.0[2]
Amgen ❑ Hoffmann-La Roche, Kirin Brewery, Sankyo	Recombinant granulocyte colony-stimulating factor (G-CSF)	Filgrastim ❑ Neupogen, Gran (Japan)	Neutropenia	1,060.0[2]
Glaxo Wellcome	5HT-3 antagonist	Ondansetron ❑ Zofran	Prevention of chemo-therapy-induced nausea	619.8 (380.3)[2]
Immunex	Recombinant granulocyte macrophage colony-stimulating factor (GM-CSF)	Sagramostim ❑ Leukine	Neutropenia	52.7
Ortho Biotech/Janssen Cilag (Johnson & Johnson)	Recombinant erythropoietin *(ibid)*	Erythropoietin α (EPO) ❑ Procrit	Chemotherapy-induced anemia	1,170.0[2]
SmithKline Beecham	5HT-3 antagonist	Granisetron ❑ Kytril	Prevention of chemo-therapy-induced nausea	366.0 (240.0)[2]
U.S. Bioscience ❑ Alza (USA), Schering-Plough (abroad)	Organic thiophosphate; selective cytoprotective agent	Amofistene ❑ Ethyol	Platinum-based chemotherapy	(20.6)

[1] Nearly 50% of Intron A revenues are derived from oncology indications
[2] A significant percent of revenues is derived from non-oncology indications
Source: NEW MEDICINE Oncology KnowledgeBASE (nm/OK), June 1998.

randomized. A total of 44 patients were randomized; 22 to capecitabine and 20 to paclitaxel. There were 8/22 (36%): responses on capecitabine, including 3 CR, and 4/19 (21%) on paclitaxel with no CR. Median time to progression was 92 days on capecitabine (44-202 days) and 95 days on paclitaxel (77-182 days). Grade 3/4 events were reported by 22% patients on capecitabine and 58% on paclitaxel. Grade 3/4 neutropenia was observed primarily with paclitaxel (68% versus 18%). While prematurely discontinued for recruitment reasons, this study illustrates that home-based therapy with capecitabine is of comparable efficacy to paclitaxel and is better tolerated (O'Reilly, SM, etal, ASCO98. Abs. 627:163a).

In an international multicenter phase II clinical trial, 109 patients with advanced colorectal cancer were randomly assigned to one of three dosing schedules of capecitabine, continuous daily treatment with 1331 mg/m^2 (group A), intermittent daily treatment with 2510 mg/m^2 (group B), or intermittent daily treatment with 1657 mg/m^2 plus LV 60 mg/day, orally (group C). The aim of the study was to evaluate the safety and efficacy of each schedule. Overall, 108 patients were evaluable for response in the three treatment schedules (39 in group A, 34 in group B, and 35 in group C). Confirmed tumor response was seen in 20.5% of those in group A (2 CR + 6 PR), 24% in group B (1 CR + 7 PR), and 22.8% in group C (2 CR + 6 PR). Median time to disease progression was 18 weeks, 33 weeks, and 24 weeks, respectively. Toxicity was mild to moderate in all but one patient, with the most common side effects being diarrhea, GI complaints, and stom-atitis. No Grade 3 hematologic toxicities were encountered (Findlay MPN, etal, ASCO97, Abs. 798:227a).

In the neoadjuvant setting, 19 patients with colorectal cancer requiring surgical resection of primary tumor and/or liver metastasis, were treated with capecitabine (1255 mg/m^2) *bid* for 5 to 7 days before surgery. On the day of surgery, samples of tumor, adjacent healthy tissue (at least 0.8 g) and blood were taken within 2 to 12 hours after the last capecitabine administration. Concentrations of 5-FU in tissues were measured and the ratio of 5-FU concentration in tumor to healthy tissue (THR), was used as a marker for tumor selectivity. The mean value of the THR was 2.9 with a range of 0.5-8.0 in the first 13 patients. Thus, results obtained in colorectal cancer indicate a high tumor selectivity after oral administration of capecitabine (Schuller J, etal, ASCO 1997, Abs 797:227a).

Fareston

Toremifene (Fareston; Orion) was approved in Europe in 1996 and in the USA in May 1997 for treatment of metastatic breast cancer, where it is marketed by Schering-Plough.

Femara

Letrozole (Femara; Novartis), that was approved and launched in the UK, its first market in November 1996, obtained FDA approval in July 1997, and was launched in the USA in September 1997, as second-line treatment of advanced breast cancer in postmenopausal women who failed antiestrogen therapy. Letrozole appears to be significantly superior to megestrol acetate (Megace; Bristol-Myers Squibb) in this setting, in terms of objective response rates, duration of response, time to treatment failure, and tolerability. Approval was based on results from large phase

III clinical trials that compared daily oral letrozole with oral megestrol acetate (160 mg) (Leonard R, etal, Breast Cancer Research and Treatment, 4(3), 1996, 220:5) or twice daily oral aminoglutethimide (250 mg) with corticosteroid supplementation. The overall objective response rate (CR + PR) was 23.6% for daily letrozole (2.5 mg), compared to 16.4% for megace and 17.6% for letrozole compared to 12.3% with aminoglutethimide. Median survival time was 731 days with letrozole compared to 660 days in the megace arm and 792 days with letrozole compared to 592 with aminoglutethimide.

Intron A

In November 1997, the FDA approved recombinant interferon α-2b (Intron A; Schering-Plough), in combination with anthracyclines, for the additional indication for treatment of low-grade, high tumor burden, follicular NHL. Intron A was approved in December 1995 as an adjuvant to surgery in patients at high risk for systemic recurrence of malignant melanoma.

Neumega

Neumega (IL-11, oprevelkin), under development by Genetics Institute (Cambridge, MA), was approved in November 1997, and launched in the USA in January 1998, for prevention of severe thrombocytopenia and to reduce the need for platelet transfusions following myelosuppressive chemotherapy in adult patients with nonmyeloid malignancies who are at high risk of severe thrombocytopenia. It is estimated that approximately 25% of all patients treated with chemotherapy are candidates for IL-11 support which translates to about 200,000 patients and 500,000 patient-cycles. Cost per course of therapy is $1,500, comparable to that of platelet infusion. Neumega is also being investigated in pediatric patients undergoing combination chemotherapy with ifosfamide, cisplatin and topotecan and is in phase II clinical trials for the treatment of mucositis.

Neupogen

The BLA for the granulocyte colony-stimulating factor (G-CSF) filgrastim (Neupogen; Amgen) was approved in April 1998 for treatment of acute myelogenous leukemia (AML). Neumega reduces time to neutrophil recovery and fever duration following induction or consolidation chemotherapy in adult AML and, also, significantly reduces use of antibiotics and hospitalization. Median hospitalization period was 20 days with Neupogen compared to 25 days otherwise, and median duration of non-prophylactic antibiotics was 15 days versus 18.5 days. However, Neupogen did not show a survival benefit.

The granulocyte macrophage colony-stimulating factor (GM-CSF) sargramostim (Leukine; Immunex) was approved in December 1995 for treatment of AML patients >55 years-of-age undergoing induction therapy, based on a superior survival endpoint at 30 days post-treatment (92% versus 72%). However, the drug was not found useful during the consolidation phase of chemotherapy.

Use of CSF for AML in elderly patients remains controversial and, in the absence of definitive ASCO guidelines and/or convincing evidence of benefit from clinical trials, physicians are mixed in their support for CSF use in elderly AML patients. A survey of American oncologists and hematologists, conducted in 1997, to establish preferences for CSF use during induction and consolidation chemotherapy for a 67 year old AML patient, elicited a response rate of 60%. For induction chemotherapy, support for not using CSF was similar to that for using CSF (42% versus 40%). It seems familiarity with CSF was a determinant of use. For instance, preference of CSF use during consolidation chemotherapy was 1.5 times more likely among those using CSF during induction chemotherapy. Also physician affiliation and specialty played a role in use patterns. Higher rates of CSF use were noted among fee-for-service rather than academic/HMO settings (15% higher) or among hematologists or hematologists/oncologists versus oncologists (15% higher). Other factors with smaller differences in favor of CSF use, included being in a practice without CSF guidelines; having been in practice <3 years, seeing >5 new cancer patients per week or having graduated from medical school before 1970 (Bishop MR, etal, ASCO98, Abs. 76:21a).

Photofrin

In January 1998, the FDA cleared Photofrin, a photodynamic approach under development by QLT PhotoTherapeutics (Vancouver, Canada), as a potentially curative treatment for certain types of early-stage, microinvasive (having invaded beyond the basement membrane but not through or into cartilage) endobronchial nsclc in patients who are not candidates for surgery and/or radiotherapy. A palliative indication in nsclc was not recommended by ODAC in September 1998 and did not gain FDA approval. Photofrin has been approved and launched for several other indications worldwide, including late stage esophageal cancers (see FO, pp 271-272).

Proleukin

In January 1998, the FDA approved Chiron's (Emeryville, CA) supplemental BLA for recombinant human interleukin-2 (rh IL-2, aldesleukin, Proleukin) as monotherapy for treatment of metastatic melanoma after the Biological Response Modifiers Advisory Committee (BRMAC) to the FDA unanimously recommended approval in December 1997. Proleukin has been approved for treatment of metastatic renal cancer in the USA, Canada and 10 other countries, and is being investigated in other malignancies alone or in combination with other agents. Proleukin is also being studied in combination with chemotherapy and interferon α for this indication.

Prolonged low-dose IL-2 therapy is also well tolerated and immunomodulatory in patients with AIDS-related malignancies. In a phase II clinical trial, low-dose Proleukin (1.2×10^6 U/m^2) was administered subcutaneously, daily, for 90 consecutive days, in patients with CR or

stable disease at entry. After 21 days rest, patients could be re-entered to be treated with additional courses of therapy. Of 25 courses administered to 19 patients, 5 were non-evaluable because of to non-compliance and, in another 5, dose was reduced to 0.9 x 10^6 U/m^2 because of Grade 3 toxicity (lethargy and myalgias). Among 8 evaluable patients with Kaposi's sarcoma, disease stabilized in 3 and progressed in 5. Among 5 evaluable patients with lymphoma, there were two responses and disease stabilized in 3. In one patient who remained on the study the longest (4 courses), residual lymphoma was resolved completely with treatment. No opportunistic infections were observed during the trial. In view of the results, rh IL-2 therapy is well tolerated in this population and appears to be effective in maintaining disease response in individuals with lymphoma (Bernstein ZP, etal, ASCO98, Abs. 207:53a).

Quadramet

Samarium SM 153 EDTMP (Quadramet; Cytogen) was approved by the FDA in March 1997 for pain relief in osteoblastic metastatic bone lesions. In June 1998, the licensing agreement between DuPont Merck and Cytogen, entered in December 1994, was terminated. At that time DuPont Merck (now DuPont Pharmaceuticals) made an additional payment for Quadramet, totaling $3.8 million. Cytogen is seeking a new partner while it is anticipated that DuPont will manufacture Quadramet over the next two years. Cytogen is expanding its own sales efforts to include Quadramet.

NEW CHEMOTHERAPEUTICS DRUGS AWAITING IN THE WINGS

There are numerous agents in late-phase clinical trials. Although none to date appear to be the elusive cancer cure, many will probably be approved for selected indications based on tumor response rates that appear to either extend survival somewhat, or improve QoL, or both.

Denileukin diftitox

In April 1998, ONTAK or DAB_{389}IL-2, an IL-2 protein fusion toxin, under development by Ligand Pharmaceuticals (San Diego, CA), was recommended for approval by a specially-convened advisory panel of oncologists, biologics experts, dermatologists and a cutaneous T cell lymphoma (CTCL) expert, for treatment of adult patients with recurrent or persisitent CTCL. ONTAK has been assigned orphan drug status for treatment of CTCL. This agent was originally developed by Seragen (Hopkinton, MA) that was acquired by Ligand in 1998.

Emitefur

The novel thymidylate synthase inhibitor emitefur (BOF-A2), under development by Otsuka (Tokyo, Japan), is composed of 1-ethoxymethyl 5-fluorouracil (EM-FU), a slow release form of 5-FU, and 3-cyano-2,6,-dihydropyrimidine (CNDP), which inhibits 5-FU degradation. In 1997, Otsuka filed for approval in Japan for treatment of advanced colorectal cancer. In a phase I clinical trial, emitefur and leucovorin demonstrated activity in refractory colorectal cancer (Matei C, etal, ASCO98, Abs. 882:230a).

Oxaliplatin

Oxaliplatin (L-OHP, Eloxatin; Sanofi), a diaminocyclohexane platinum compound, originally developed by Debiopharm (Lausanne, Switzerland) and subsequently licensed to Sanofi for the USA and European markets, has been primarily evaluated abroad and was launched in France in 1996 as a second-line hospital-based treatment for metastatic colorectal cancer. In April 1998, L-OHP was also approved in France for the additional indication as first-line treatment of metastatic colorectal cancer, either as monotherapy or in combination with fluoropyrimidines such as 5-FU. In 1998, Sanofi expects to file for approval of L-OHP in the USA and in the rest of Europe for both of these indications. L-OHP is being investigated for other indications such as ovarian and breast cancer. L-OHP is the first compound of its class to reach the market and the first platinum-based agent demonstrating efficacy in colorectal cancer, suggesting that it may have a different mode of action than currently used platinum agents. For instance, L-OHP exhibits partial or no cross-resistance with cisplatin and carboplatin in preclinical *in vitro* or *in vivo* models.

In a preclinical trial, investigators at the Centre de Chronotherapie (Villejuif, France) assessed the toxic effects of 5-FU and L-OHP in metastatic colorectal cancer in mice or rats and found that they varied by 50% or more according to circadian dosing time. Also, Wistar rats, L-OHP exhibited reduced neurotoxicity than cisplatin and ormaplatin (Holmes J, etal, AACR97, Abs. 22:4). Chemotherapy delivery of L-OHP according to circadian rhythms (chronotherapy) was subsequently assessed in fully ambulatory outpatients, using multichannel programmable pumps (Levi F, etal, European Journal of Cancer, 1995 Jul-Aug, 31A(7-8):1264-70). First, single- agent, 5-day chronomodulated schedules were devised and assessed in phase I and II clinical trials with 5-FU (peak delivery at 4:00 hours) or L-OHP (peak delivery at 16:00 hours). Both schedules were then combined and folinic acid (FA) was added synchronously with 5-FU infusion. This three-drug chronomodulated regimen (chrono-FFL) resulted in an overall response rate of 58% in 93 patients with metastatic colorectal cancer, 46 of whom were previously treated with chemotherapy.

In the first European randomized clinical trial, in 92 previously untreated patients, chronomodulated three-drug delivery achieved a 53% response, as compared to 32% in patients treated with standard infusion. A subsequent multicenter randomized clinical trial involving 186 additional patients, confirmed these figures. Because the most active schedule was also the least toxic (2- to 10-fold), chrono-FFL was further intensified in three consecutive phase II trials involving a total of 200 additional patients. Results suggest chrono-FFL more than doubled the activity of chemotherapy against metastatic colorectal cancer; both

response rate and QoL were further improved with such treatment intensification.

A phase II/III randomized study of 5-FU/leucovorin (5-FU/LV) with versus without oxaliplatin, is being evaluated in inoperable metastatic colorectal cancer (FRE-DEB95-OXA-01) and colorectal cancer resistant to 5-FU and leucovorin alone (FRE-FOLFOX-3-4), at the Hôpital Saint Antoine (Paris, France) by the Groupe d'Etude et de Recherche sur les Cancers de l'Ovaire et Digestifs (GERCOD). In phase I clinical trials it appeared that oxaliplatin may potentiate 5-FU at the tumor level (Gamelin E, AACR97, Abs. 1500:223). In a phase I clinical trial conducted in France, L-OHP in combination with CPT-11, was also found to be active in advanced gastrointestinal cancer (Lokiec F, AACR97, Abs. 514:76). Also see FO, p 331.

According to preliminary results from a phase II clinical trial, performed in France, L-OHP monotherapy produced an overall response rate of 30% in pretreated advanced ovarian cancer with a good tolerance profile. L-OHP (130 mg/m^2) was administered as a 2-hour IV infusion on day 1, every 3 weeks until progressive disease or limiting toxicity. Among 40 patients enrolled as of November 1997, 30 were evaluable for efficacy (17 platinum-sensitive and 13 refractory). Among 17 platinum-sensitive patients, there was 1 (5.9%) CR, 7 (41.2%) PR, 4 (23.5%) MR, and disease stabilized in 4 and progressed in 1 and, among 13 patients who were platinum-refractory, there was 1 PR and disease stabilized in 4 and progressed in 8 (Dieras V, etal, ASCO98, Abs. 1405:364a). A phase II (protocol ID: EORTC-55951) randomized clinical trial is also evaluating L-OHP and paclitaxel in platinum-pretreated advanced ovarian cancer. Also see FO, p 571.

Raltitrexed

Raltitrexed (ZD1694, Tomudex; Zeneca), a folate-based quinazoline selective thymidylate synthase inhibitor, is a "British" drug developed in collaboration with the Institute of Cancer Research (London, UK). Since its commercial introduction in the UK in 1996 for treatment of chemotherapy-naive advanced colorectal cancer, it has been well received in Europe where it is used extensively. The drug was shown to have an acceptable safety profile and a similar response rate to 5-FU and LV in advanced colorectal cancer but lower toxicity. Also, the administration schedule of ralitrexed, an injectable, is less cumbersome than that of 5-FU.

Zeneca, having submitted an NDA in 1997, is gearing up to market the drug in the USA in anticipation of a favorable review. Zeneca's NDA filing was delayed in the USA because, in one large North American trial comparing raltitrexed with 5-FU/LV in advanced colorectal cancer, time-to-disease progression and overall survival were significantly longer for those treated with 5-FU and leucovorin (see FO, pp 622). In a similar European phase III clinical trial of raltitrexed, randomized against a 5-FU plus leucovorin regimen, an equivalent response rate (CR + PR) for advanced colorectal cancer (20% versus 17%) was achieved but toxicity was lower with the latter regimen. Of 439 previously untreated patients with advanced colorectal cancer, 222 were randomly assigned to Tomudex (3 mg/m^2) and leucovorin (20 mg/m^2), administered as an IV bolus daily, for 5 days, repeated every 4 to 5 weeks, and 217 to conventional therapy. Overall objective response rates were 20% for Tomudex and 16.5% for conventional therapy. Median time to disease progression was 4.9 months and 3.5 months, respectively, while MST was 10.3 months and 10.5 months, respectively. Higher rates of Grade 3/4 leucopenia occurred in 14% (Tomudex) and 30% (5-FU/LV) of patients, and mucositis occurred in 2% and 22%, respectively. There was also a much higher incidence of alopecia among those treated by 5-FU/LV (Seitz JF, etal, ASCO96, Abs. 446:201). Tomudex is also currently in clinical trials in colorectal cancer in combination with irinotecan, L-OHP, paclitaxel or 5-FU. Tomudex is also being evaluated in breast cancer (see FO, pp 481).

UFT

UFT, developed by Taiho Pharmaceutical (an Otsuka group company) and licensed to Bristol-Myers Squibb in the USA and other markets, is a fixed-ratio combination of uracil and tegafur (Ftorafur), a prodrug that is absorbed orally and metabolized *in vivo* to 5-FU (see FO, pp 55 and 481). Uracil potentiates 5-FU through interference with its catabolism. The clear advantage of UFT appears to be its administration route. When evaluated in the elderly, in the neoadjuvant setting, as an adjuvant, and in combination with other drugs, UFT appears to be as effective and as well tolerated as 5-FU. UFT's overall performance and BMS' marketing clout may propel this drug into a significant market performer.

The leading indication under development for UFT is advanced colorectal cancer. BMS began a 600-patient phase III trial for the colorectal cancer indication in June 1995 at 60 centers in the USA and Europe, managed by Theradex (Princeton, NJ).

In one clinical trial, conducted by the Oncopaz Cooperative Group in Spain between January 1992 and December 1995, 269 consecutive patients with resected Dukes' Stage B2-C colon cancer were treated with 12 courses of adjuvant chemotherapy (6 courses since June 1995), consisting of a 2-hour IV infusion of leucovorin (500 mg/m^2) on day 1, followed by oral leucovorin (12 mg) every 12 hours, on days 2 to 14, and UFT (390 mg/m^2) administered in 2 daily doses, on days 1 to 14, repeated every 28 days. Although 72% of patients stayed on the schedule, 42% required dose reduction because of toxicity usually consisting of diarrhea and, less often, of other gastrointestinal symptoms. There were no toxic deaths. After a median follow-up of 36 months (1-89), 42 patients relapsed (25%) with the main sites of relapse being the liver (16), colon (12) and lung (7). Relapse was not related to reduced doses or early termination of chemotherapy. Relapse rates for stages B2 and C were 11% and 30%, disease-free survival was 83% and 62%, and the overall survival was 94% and 87%, respectively (Espinosa E, etal, ASCO98. Abs. 1059:275a).

In a phase III randomized clinical trial, conducted in Hong Kong, the efficacy of UFT was evaluated as maintenance therapy after completion of standard adjuvant chemotherapy in colorectal cancer. Between July 1991 and July 1995, 140 patients who had completed adjuvant chemotherapy were enrolled and half were treated with UFT (200 mg) *bid* for 1 year after adjuvant chemotherapy with the rest remaining under observation. The 5-year overall survival and disease-free survival for the UFT arm versus control arm were 61.0% versus 56.0%, and 59.0% versus 52.0% respectively. Therefore, a prolonged course of oral UFT after standard adjuvant chemotherapy does not improve survival of Dukes' B and C colorectal cancer patients (Mok TSK, etal, ASCO98, Abs. 1042:271a).

A repeatable schedule consisting of 5 days of UFT (600 mg/day) and two drug free days which results in almost the same weekly dose as conventional daily administration of UFT (400 mg/day), was designed based on animal studies (ASCO97, Abs. 726:207a) and conducted in 11 centers by the UFT Compliance Study Group (Kanagawa, Japan). This new schedule was used for one year as adjuvant chemotherapy for curatively resected colorectal in 91 patients enrolled between March 1995 to March 1996, of whom 87 were evaluable. Patient compliance was determined by interviews and questionnaires, and by monitoring individual dose intensity and by random measurement of urinary tegafur levels. Adverse effects, experienced by 31 patients (35.6%), consisted of nausea/ vomiting (11.5%), liver dysfunction (9.2%) and diarrhea (6.9%), but none were serious (Sadahiro S, etal, ASCO98, Abs. 1054:1052).

In a neoadjuvant setting, UFT was used instead of protracted 5-FU infusion, to treat rectal cancer in conjunction with radiotherapy before surgery. In a phase I clinical trial conducted M. D. Anderson Cancer Center, patients with Stage II and III rectal carcinoma were treated with radiotherapy (4500 cGy) and concomitant oral UFT combined with IV leucovorin (30 mg), administered every 8 hours daily, for 5 days each week during 5 weeks, followed 4-6 weeks later by surgery. Four to six weeks postoperatively, patients were treated with adjuvant UFT/LV for 28 days, every 35 days, for 4 courses. Three patients were entered at three different UFT dose levels. Among 6 evaluable patients, 3 at UFT level 1 (250 mg/m^2) and 3 at level 2 (300 mg/m^2), there was one CR at each level. All 5 of these patients who underwent sphincter-sparring procedures were disease-free at 5-8 months follow-up. No Grade 4 toxicity was observed. Grade 3 diarrhea occurred in one patient at the 300 mg/m^2 dose level (Hoff PM, etal, ASCO98, Abs. 860:223a).

Many UFT clinical trials are ongoing in Japan where the drug is the most commonly prescribed anticancer. UFT is being studied as a replacement for 5-FU in a 3 times weekly regimen of epirubicin, cisplatin and protracted IV 5-FU which is a highly active combination in various advanced solid tumors. In a phase I/II clinical trial, being conducted in the UK, 5-FU is being replaced with UFT at escalating doses, together with weekly folinic acid in patients with advanced upper GI cancer (Seymour MT, etal, ASCO98, Abs. 996:259a). Other indications for UFT include:

- in combination with a platinum-based agent in chemotherapy-naive advanced nsclc or advanced head and neck cancer
- as monotherapy in Stage II, III, or IV gastric cancer
- in combination with a platinum-based agent and epirubicin in upper gastrointestinal cancer

NOVEL TREATMENTS

The success of newly introduced anticancer agents, including their ability to command high prices in most parts of the developed world, has spurred the development of numerous novel antitumor agents arising from every imaginable source. According to nm|OK, among the nearly 1,000 anticancer agents in development, at least 371 are in clinical trials, most (91%) in phase I or phase II. Because many of these agents are being investigated for more than one indication and by separate groups, there are even more clinical trials in progress.

MONOCLONAL ANTIBODIES COME OF AGE

According to nm|OK, as of mid-1998, there were at least 92 different agents in development incorporating MAbs. Rituxan, approved by the FDA in late 1997, may have paved the way for other MAb-based agents, some in late stages of clinical development, consisting of either naked MAbs or MAbs conjugated to drugs, radioisotopes or toxins.

Rituxan

Rituxan (rituximab, IDEC-C2B8) is a chimeric murine/human MAb that targets the CD20 antigen expressed on normal and malignant B cells and on >95% of B cell non-Hodgkin's lymphoma (NHL). Rituxan was approved by the FDA for relapsed or refractory B cell NHL in November 1997, it was launched in December 1997. Originally developed by IDEC Pharmaceuticals (San Diego, CA) it is currently marketed by Genentech (South San Francisco, CA) in the USA and Hoffmann-La Roche abroad. Rituxan costs about $8,904 per course of treatment in the USA. It generated sales of $37.7 million ($35.2 million in the USA) in its first full quarter compared to $5.5 million in its first month of sales in 1997. Outside the USA, as of mid-1998, it was only launched by Roche in Switzerland. Worldwide sales are estimated to reach $175 million in 1998. USA sales are forecast to reach $300 million in 1999 and $395 million in 2000. Numerous additional trials are ongoing. In clinical trials in relapsed low-grade B cell NHL, rituximab demonstrated a 50% response rate. Also, its toxicity profile did not overlap that of combination chemotherapy. In preclinical trials, *in vitro,* rituximab's mechanisms of action include complement dependent cytotoxicity, antibody dependent cellular cytotoxicity and apoptosis.

A phase II clinical trial was conducted in patients with previously untreated intermediate or high-grade B cell NHL to assess the effectiveness of Rituxan in combination with

chemotherapy. Patients were treated with rituximab (375 mg/m^2) on day 1 of each 21-day cycle, followed 48 hours later by a CHOP regimen consisting of cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2) and vincristine (1.4 mg/m^2), all on day 3, and prednisone (100 mg) on days 3-7. Thirty-one patients with various stages of B cell NHL were treated with six cycles of therapy. Grade 4 neutropenia occurred in 13 patients (17 cycles), Grade 3 neutropenia in 16 cycles, dehydration in 2 patients (4 cycles), asthenia in 3 patients, abdominal pain/back pain in 2 patients each, and intestinal obstruction, hypersensitivity, arthralgia/arthritis, anorexia, diarrhea, nausea/vomiting and anemia in 1 patient each. Other Grade 1/2 toxicities were those expected with CHOP or rituximab. There were no deaths. Among 30 patients evaluable for response, there were 19 CR (63%), 10 PR (33%), and one progression. Serious adverse events with this therapy occurred with a frequency similar to that seen with conventional CHOP alone but response rates were higher (Link BK, etal, ASCO98, Abs. 7:3a).

Rituximab (375 mg/m^2), administered weekly for weeks 5-8, is also being investigated in combination with subcutaneous interferon α (Roferon A; Hoffmann-La Roche) at 5 million units per day, 3 times weekly, for three months in the treatment of relapsed or refractory low-grade or follicular NHL. According to an interim analysis performed on 31 patients, adverse events were primarily Grade 1 or 2 toxicities occurring with the first infusion. Seven patients required dose modification and interferon was discontinued in 2. There were no deaths. Among 26 evaluable patients there were 2 (8%) CR and 13 (50%) PR for an overall response rate of 58%. There were 2 additional minor responses and disease stabilized in 5 (Davis T, etal, ASCO98, Abs. 39:11a).

In June 1998, Hoffmann-La Roche was granted marketing authorization by the European Commission for rituximab (MabThera) in the treatment of relapsed or chemoresistant follicular B cell NHL in all European Union (EU) countries. MabThera will be available initially in the UK and Germany, with launch in other member states of the EU to follow soon afterward. Roche previously received marketing clearance for MabThera from the Swiss Regulatory body IKS (Interkanthonale Kontrollstelle fÅr Heilmittel) in November 1997.

HER2 MAb-based Agents

Herceptin (trastuzumab), under development by Genentech, is a humanized MAb that targets the 25% to 30% of breast tumors that produce HER2/neu protein. In July 1998, Roche announced that it obtained exclusive marketing rights outside the USA for Herceptin. According to the agreement Roche will pay a substantial up-front fee, cash milestones tied to product development activities, contribute equally with Genentech to global development costs, and make royalty payments on product sales. In addition to metastatic breast cancer, the agreement also includes a joint global development program for other solid tumors such as nsclc.

Herceptin is active as monotherapy in metastatic refractory HER2-expressing breast cancer with a response rate of approximately 15%. In a an international multicenter open-label phase III clinical trial, conducted between April 1995 and September 1996, 222 women with relapsed refractory HER2-overexpressing metastatic breast cancer, were treated IV with Herceptin at a loading dose of 4 mg/kg and a weekly dose of 2 mg/kg. At a median follow-up of 11 months, among 213 evaluable patients, the overall response rate (CR + PR) was 15%, with 6 confirmed CR and 25 PR; median duration of response was 8.4 months and MST was 13 months. A reduction in cardiac ejection fraction was observed in 9 patients who were either treated with prior anthracycline therapy or had significant cardiac history at entry; 6 of these patients were symptomatic and one woman died of a ventricular arrhythmia (Cobleigh MA, etal, ASCO98, Abs. 376:97a).

Herceptin also augments the activity of standard chemotherapy. Half of 469 patients with HER2+ metastatic breast cancer being treated with 6 cycles of standard chemotherapy [doxorubicin and cyclophosphamide or paclitaxel (175 mg/m^2 over 3-hours) as first-line therapy, if they had not been previously treated with adjuvant doxorubicin, or paclitaxel, if previously exposed to doxorubicin] were randomized to Herceptin (4 mg/kg loading, then 2 mg/kg IV every week). At a median follow-up of 10.5 months, time to disease progression (TTP) and response rates showed a significant therapeutic augmentation by Herceptin, without increase in overall severe adverse events. Overall, response rate increased from 36.2% to 62%, a 71% improvement with the addition of Herceptin (n=235) but was more pronounced in the paclitaxel-treated group (n=89) where it jumped from 25% to 57.3%, a 129.2% improvement. TTP for all groups was 8.6 months with Herceptin compared to 5.5 months with standard treatment but again it was most pronounced in the paclitaxel group, rising from 4.2 months to 7.1 months. Furthermore, at one year, there was no evidence of progression of disease in 28% of women on Herceptin plus chemotherapy versus 14% of those treated with chemotherapy alone. In addition, Herceptin plus chemotherapy resulted in objective response rates of 49% (114/235) compared to 32% (74/234). However, a Grade 3/4 syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported with the Herceptin, doxorubicin and cyclophosphamide combination (18%) that was less common with the doxorubicin and cyclophosphamide combination alone (3%), paclitaxel alone (0%), or paclitaxel and Herceptin (2%) (Slamon D, etal, ASCO98, Abs. 377:98a).

The documented increased cardiac risk with Herceptin marred its otherwise benign side effects profile. Investigators are baffled as to the origin of this toxicity. A study being conducted in women who had not been previously exposed to anthracyclines, commonly associated with cardiotoxicity, may decide if this cardiotoxicity is related to previous anthracycline exposure or is somehow attributable to Herceptin.

While Genentech is awaiting approval for Herceptin, currently on FDA's fastrack program, it is working with the National Cancer Institute (NCI) to make the drug available for testing in larger numbers of breast cancer patients and in more places around the country. Currently, because of limited supplies, patients meeting eligibility criteria are selected by lottery to become part of a non-randomized study. NCI, through its Treatment Referral Center program representing 50 NCI-designated cancer centers around the country, is also arranging to have the drug available in more locations than the ten different hospitals where it was originally available.

NCI is also working with Genentech to study Herceptin at different stages of breast cancer and in combination with other agents. These new breast cancer trials could start enrolling patients in mid-1998. These trials will be carried out by NCI's cooperative clinical trial groups and by investigators in other NCI-sponsored centers. NCI is also collaborating with Genentech to expand studies of Herceptin for other indications and uses. NCI-sponsored cooperative clinical trial groups and Genentech are already working together in two clinical trials, one phase I/pilot study of Herceptin in combination with low-dose IL-2 in a variety of solid tumors, being conducted by NCI's Cancer and Leukemia Group B (protocol ID: CALGB-9661), and a phase II study of Herceptin in recurrent or refractory ovarian or primary peritoneal carcinoma, being conducted by the Gynecologic Oncology Group (Protocol ID: GOG-160).

Once there is an adequate drug supply, NCI and Genentech plan to evaluate Herceptin in a variety of malignancies, including gastric, endometrial, salivary gland, non-small cell lung, pancreatic, prostate, and colorectal cancers that overexpress HER2, estimated at 30% to 40% of these tumor types.

Herceptin is expected to be approved in the USA by the end of 1998. Selection of patients is now also possible by using the Oncor (Gaithersburg, MD) INFORM HER-2/neu test that uses a fluorescence *in situ* hybridization (FISH) DNA probe assay to determine the qualitative presence of HER2/neu gene amplification on formalin-fixed, paraffin-embedded human breast tissue, that was approved by the FDA in December 1997. Analysts estimate that Herceptin, if launched in 1999, will generate revenues of $225 million in 2001.

Other HER2 MAb-based agents are in development, using HER2 to select and target cancer cells.

Medarex (Annandale, NJ), in collaboration with Merck KGaA, is developing MDX-H210 (see FO, pp 489-90), in phase I and II clinical trials in the USA and abroad, for various tumors that overexpress HER2/neu. In the case of MDX-H210, the mechanism of antitumor action is antibody-dependent cellular cytotoxicity (ADCC).

2B1, a bispecific murine MAb that affects lysis of tumor cells expressing c-erbB-2 (HER2) protein, in development by Chiron (Emeryville, CA), is in clinical trials being sponsored by the NCI. In a multicenter phase Ib/II clinical trial (protocol ID: E-3194) in metastatic breast cancer, being conducted by the Eastern Cooperative Oncology Group (ECOG), up to 32 evaluable patients will be entered over 2 years if at least 1 objective clinical response is seen in the first 18 evaluable patients. In a phase Ia/Ib clinical trial (protocol IDs: FCCC-96047, NCI-B95-0002), expected to accrue 26-36 patients over 29 months, 2B1 is being is evaluated in combination with GM-CSF/IL-2.

RANTES.Her2.IgG3, a fusion of HER2 MAbs with the chemokine RANTES, a potent chemoattractant of T cells, NK cells, monocytes and dendritic cells, is being investigated as an immunotherapy approach by researchers at the University of Rochester Cancer Center (NY) and UCLA. RANTES.Her2.IgG3, alone or in combination with other chemokine or cytokine fusion MAbs, may recruit and activate a variety of effector cells against breast, ovarian and/or other tumors (Challita-Eid PM, etal, ASCO98, Abs. 1685:437a and AACR98, Abs. 2975:437).

In an interesting approach, researchers at the University of California, San Francisco (UCSF), in collaboration with the NCI, have combined the tumor targeting capabilities of certain HER2/neu MAbs with the pharmacokinetic and drug delivery properties of sterically stabilized liposomes, to develop anti-HER2 immunoliposomes (ILs) to be used as delivery vehicles for doxorubicin. Anti-HER2 ILs efficiently bind to and internalize in HER2-overexpressing cells *in vitro*, resulting in intracellular drug delivery. Doxorubicin-loaded ILs (ILs-dox) greatly increase the *in vivo* therapeutic index of doxorubicin, by increasing its antitumor efficacy and by reducing its systemic toxicity. Anti-HER2 ILs-dox produced significant therapeutic effects such as growth inhibition, regressions, and cures, in four different HER2-overexpressing tumor xenograft models. Cure rates for ILs-dox were 50% (11/21) in Matrigel-free tumors, and 16% (18/115) for all tumor models, versus no cures (0/124) with free or liposomal doxorubicin. ILs-dox was significantly superior to all other treatments tested, including free doxorubicin, liposomal doxorubicin, anti-HER2 MAb (rhuMAbHER2) alone, and free doxorubicin in combination with rhuMAbHER2. For example, in 8 separate studies comparing ILs-dox to liposomal doxorubicin, ILs-dox yielded significantly superior efficacy and ILs-dox containing rhuMAbHER2-Fab' or C6.5, an anti-HER2 scFv, yielded comparable therapeutic efficacy. Although, it appears that both ILs and liposomes accumulate at extremely high levels in BT-474 tumor xenografts *in vivo*, reaching 7-8% injected dose/g tissue, there is a dramatic difference in distribution and mechanism of delivery between these two approaches. ILs are dispersed throughout the tumor, and, notably, are predominantly observed within the cytoplasm of tumor cells while, in contrast, liposomes accu-

mulate extracellularly or within macrophages. These results confirm that ILs, unlike liposomes, achieve intracellular drug delivery which may account for their significantly enhanced efficacy (Park JW, etal, ASCO98, Abs. 833:216a).

Radioimmunoconjugates

According to nm|**OK**, radioimmunoconjugates for *in vivo* imaging and therapeutic applications comprise about 20% of all MAb-based antitumor agents in development, with several having reached late stage clinical trials. Bexxar, an iodine-131 anti-B1 antibody conjugate (see FO, p 758), under development by Coulter Pharmaceutical (Palo Alto, CA), is in phase II clinical trials in NHL, as is IDEC-Y2B8, a MAb/yttrium-90 construct, under development by IDEC Pharmaceuticals. Theragyn, a yttrium-90 labeled murine IgG1 MAb (HMFG1) under development by Antisoma (London, UK), just entered phase III clinical trials abroad for the treatment of ovarian cancer.

PREVENTION/TREATMENT OF METASTASIS

Presence and/or development of metastases is the leading cause of treatment failure, relapse and death in most cancer cases. To date, no effective agent exists that deals with this problem and, even novel agents in development targeting the putative contributors to this phenomenon, are coming up short. Exhibit 9 lists selected agents in development that appear to possess the necessary attributes to prevent tumors from spreading and/or destroy micrometastases after they have formed.

Matrix Metalloproteinase Inhibitors (MMPI)

Matrix metalloproteinases (MMPs), a family of 15 zinc endopeptidases, play a pivotal role in tumor invasion, angiogenesis and metastasis. Because malignant tumors express high levels of MMPs, inhibitors of these enzymes are viewed as promising antimetastatic agents.

Marimastat, an oral MMPI under development by British Biotech (Oxford, UK), is in phase II/III clinical trials in many indications. Considered a forerunner in this area, its outlook has been clouded by allegations of problems by the since dismissed clinical research director in charge of the marimastat clinical trials. Lately, British Biotech, has been besieged by personnel, legal and product development problems. Also, final results from trials with marimastat in solid tumors have not been reported and the drug is being hampered by excessive neurotoxicity. However, those close to this product insist that the problems have been exaggerated, the drug works as intended and results from several clinical trials in various types of tumors will be reported in 1999. Changing strategy, British Biotech also announced in 1998 that it will seek a marketing partner for marimastat in the USA.

Marimastat is in phase III clinical trials for numerous indications. As a cytostatic, however, its role may be more appropriate in combination with cytotoxic agents. Several phase I/II clinical trials are investigating marimastat in combination with 5-FU and carboplatin in relapsed ovarian cancer, doxorubicin and cyclophosphamide in metastatic breast cancer and gemcitabine in non-resectable pancreatic cancer, among others.

AG3340, a synthetic selective inhibitor of certain MMP enzymes such as gelatinase A and B, stromelysin-1 and collagenase-3, is being developed by Agouron Pharmaceuticals (La Jolla, CA). In May 1998, the company initiated two large-scale phase II/III randomized clinical trials involving 500 patients each, to be carried out in sites throughout North America. In one of these trials involving patients with advanced nsclc, AG3340 is administered in tablet form in combination with paclitaxel and carboplatin. The primary objective of this study is to compare time to progression between patients treated with AG3340 or placebo, in combination with paclitaxel and carboplatin. In the other trial, patients with advanced prostate cancer are treated with AG3340 in combination with mitoxantrone and prednisone. The primary objective of this study is to evaluate time-to-symptomatic progression of disease. Secondary endpoints for both trials include response rates, survival, and QoL measurements.

BAY 12-9566, a biphenyl MMP-2 and MMP-9 inhibitor, under development by Bayer (West Haven, CT), just entered phase II/III clinical trials involving 800 patients with solid tumors. In a phase I clinical trial, conducted in Canada, involving both treated and untreated patients, MDT of BAY 12-9566 was 400 mg *qid* or 800 mg *bid* (Goel R, etal, ASCO98, Abs. 840:217a). Unlike marimastat, that is a broad MMPI, BAY 12-9566, a selective MMPI, is associated with fewer side effects. In another phase I clinical trial conducted at the Mayo Clinic, 11 patients were treated at 400 mg *qid* or 800 mg *bid*, daily, without untoward toxicities but with no effect on surrogate markers (Erlichman C, ASCO98, Abs. 837:217a).

Inhibition of Angiogenesis and Tumor Vascularization

Angiogenesis inhibition appears to be a broad-based rational approach to treat/prevent metastasis by cutting off circulation to tumor cells and, therefore, preventing them in establishing themselves in new sites. Developments in the search for approaches that inhibit angiogenesis either by modulating intrinsic factors that promote angiogenesis or by selectively targeting and destroying tumor vasculature, have been described extensively in past issues of FUTURE ONCOLOGY (see FO, pp 746-747, 684-685, 493-494, 274-275, 269-270, 185-199).

Inhibition of angiogenesis as a cancer treatment recently became the topic of media frenzy, when a New York Times article quoted (misquoted?) two prominent scientists referring to the antiangiogenesis approach as an imminent cure for cancer. Although promising findings in this area had been extensively reported in the scientific literature and several agents with antiangiogenic properties are in early clinical trials (Exhibit 9), the press treated the

Exhibit 9
Angiogenesis Inhibitors and Matrix Metalloprotease Inhibitors (MMPIs) in Development for the Treatment of Cancer

Developer ❑ Affiliate(s)	Generic Name ❑ Number ❑ Brand Name	Description ❑ Administration Route	Status ❑ Indications
Æterna Laboratories	AE-941 ❑ Neovastat	Shark cartilage liquid extract ❑ PO	Phase III (o3/98)➢Canada ❑ solid tumors; phase I/II (o3/98)➢USA and Canada ❑ metastatic lung, prostate and breast cancer
Agouron Pharmaceuticals ❑ Hoffmann-La Roche (terminated)	AG3340	Synthetic selective inhibitor of certain MMP enzymes such as gelatinase A and B, stromelysin-1 and collagenase-3; angiogenesis inhibitor PO	Phase II/III (b5/98)➢USA, Canada ❑ advanced non-small cell lung cancer (nsclc); phase II/III (b5/98)➢USA ❑ advanced, hormone-refractory prostate cancer; phase I (c96)➢Scotland, (c97)➢USA ❑ solid tumors
Agouron Pharmaceuticals		Antiangiogenic agent that blocks KDR receptors for vascular endothelial growth factor (VEGF)	Research (4/97)➢USA ❑ solid tumors
Aronex Pharmaceuticals	AR639	Selectively inhibits VEGF production	Preclin (3/97)➢USA ❑ solid tumors
Bayer	BAY 12-9566	Biphenyl MMP-2 and MMP-9 inhibitor ❑ PO	Phase III (o98)➢USA, Canada ❑ solid tumors
BioStratum (BST)	BST-1002 (breast cancer); BST-103 (prostate cancer); BST-1004 (lung cancer)	Peptides from collagenous domains of type IV collagen which have antimetastatic properties	Preclin (5/98)➢USA ❑ solid tumors
BioStratum (BST)	BST-2001 ❑ Angiocol	Therapeutic derived from type IV collagen which mimic basal lamina domains that participate in the process of tumor invasion and migration thereby inhibiting the process; antiangiogenic	Preclin (5/98)➢USA ❑ solid tumors
Boston Life Sciences	Troponin I	Inhibitory subunit of a protein complex involved in calcium-mediated prevention of actomyosin binding and ATPase activity during skeletal muscle contraction ❑ subcutaneous	Preclin (7/97)➢USA ❑ solid tumors
Bristol-Myers Squibb (BMS) ❑ NCI, CRC Technology	Bryostatin-1 (BRYO) ❑ NSC-339555	Natural macrocyclic lactone derived from the marine bryozoan *Bugula neritina* that is a ligand and modulator of protein kinase C (PKC) ❑ IV	Phase I (b10/96, o3/98)➢USA ❑ solid tumors; phase II (o12/97)➢USA ❑ high-grade recurrent astrocytoma and recurrent high-grade mixed glioma; phase II (b3/98)➢USA myelodysplastic syndrome (MDS)
British Biotech	BB-3644	A combination inhibitor of tumor necrosis factor (TNF) and MMPs	Preclin (6/98)➢UK ❑ solid tumors
British Biotech ❑ Tanabe Seiyaku (licensee, Japan)	Marimastat ❑ BB-2516	Oral MMPI ❑ PO	Phase III (o3/97)➢USA, UK ❑ sclc, nsclc; phase I/II➢(o8/97) ❑ breast cancer; phase III (o3/97) ➢USA, UK; phase II (o2/98) USA ❑ gliosarcoma, glioblastoma multi-forme; phase III (3/97) UK ❑ pancreatic cancer; phase III (b1Q/97); phase I (c98), phase II (b98)➢UK (in combination with carboplatin) ❑ advanced refractory ovarian cancer; phase III (3/97)➢UK ❑ stomach cancer; phase I/II (o98); phase I (o5/98)➢USA ❑ solid tumors

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CarboMed ❑ NCI, Zeneca, Vanderbilt U	GBS toxin ❑ CM101, ZD0101 (Zeneca)	300 MW polysaccharide exotoxin produced by Group B Streptococcus ❑ infusion	Phase I (7/97, c97); phase II (b12/97)➢USA ❑ solid tumors
Cell Therapeutics (CTI) ❑ BioChem Pharma	CT-2584	Low molecular weight phospholipid signaling inhibitors that alter production of the intracellular second messenger, phosphatidic acid, which is involved in a variety of agonist stimulated cell growth and activation responses ❑ infusion	Phase I (b5/96, o3/98)➢UK, USA ❑ ovarian cancer, refractory prostate cancer; phase I (b11/95, o3/97)➢UK ❑ colon cancer; phase I (o3/97)➢USA ❑ sarcoma; phase I (o3/97)➢UK ❑ mesothelioma
Celltech Therapeutics ❑ Zeneca		Inhibitors of the metalloproteinase gelatinase	Research (3/98)➢UK ❑ solid tumors (an earlier gelatinase inhibitor, CDP-845, was discontinued in 1995)
Chiroscience Group ❑ Bristol-Myers Squibb	D1927	Selective against specific MMP enzymes without affecting TNF or IL-1 release, which is believed to play a key role in the inflammation process and may lead to side effects ❑ PO	Preclin (1/98) USA ❑ solid tumors
Chiroscience Group ❑ Bristol-Myers Squibb	D2163	As above	Phase I (b1/98) Europe
CliniChem Development ❑ Beth Israel Hospital, Harvard U		Angiogenesis inhibitors targeting the $\alpha(v)\beta(3)$ receptor	Preclin (2/97)➢USA ❑ solid tumors
CollaGenex Pharmaceuticals ❑ Boehringer Mannheim, NCI, U Miami, State U New York at Stony Brook	Metastat	Chemically-modified non-antimicrobial tetracycline; MMPI	IND (f12/97) ❑ solid tumors
EntreMed		Vaccination with synthetic peptide derived from the heparin-binding domain of basic fibroblast growth factor (bFGF); inhibits neovascularization	Research (3/98)➢USA ❑ solid tumors
EntreMed ❑ Children's Hospital at Harvard Medical School, Bristol-Myers Squibb	Angiostatin	Recombinant angiostatin protein; blocks new blood vessel formation	Preclin (3/98)➢USA ❑ solid tumors, malignant melanoma
EntreMed ❑ Children's Hospital at Harvard Medical School	Endostatin	Recombinant antiangiogenic protein; inhibits growth of blood vessels	Preclin (3/98)➢USA ❑ solid tumors
EntreMed ❑ Children's Hospital at Harvard Medical School, Bristol-Myers Squibb	2-methoxyestradiol (2-ME)	Natural estrogen metabolite; inhibits breast cancer cell proliferation ❑ PO	Preclin (1/97) USA ❑ solid tumors, breast cancer
EntreMed ❑ Children's Hospital at Harvard Medical School, Bristol-Myers Squibb	Thalidomide analogs	Antiangiogenic compounds ❑ PO	Preclin (1/98)➢USA ❑ solid tumors, malignant melanoma
EntreMed ❑ Children's Hospital at Harvard Medical School, NCI	Thalidomide	Antiangiogenic compound; may block certain growth factors such as bFGF and VEGF ❑ PO	Phase II (b3/96, c97)➢USA ❑ glioblastoma multiforme, anaplastic astrocytoma; phase II (6/97)➢USA ❑ Kaposi's sarcoma (KS); phase II (6/97)➢USA ❑ androgen-independent metastatic prostate cancer; phase II (1/97)➢USA ❑ breast cancer
Genentech	RhuMAB VEGF	Antagonist of VEGF ❑ IV	Phase II (b2/98)➢USA; phase I (c97; o3/98)➢USA ❑ advanced solid tumors, prostate cancer (in planning)
Genetix Pharmaceuticals ❑ Harvard Medical School and Children's Hospital, Boston		Retroviral-mediated *in vivo* gene transfer of cDNAs encoding antiangiogenic proteins Angiostatin and Endostatin; demonstrated tumor growth inhibition when introduced in murine hematopoietic cells	Preclin (6/98)➢USA ❑ solid tumors

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Glycomed (Ligand Pharmaceuticals)	GM1474, GM1306	Small sulfated carbohydrate molecule	Research (o5/98)➢USA
Glycomed (Ligand Pharmaceuticals)	GM1603 and analogs	Growth factor modulators; heparinase inhibitors; MMPI	Research (o5/98)➢USA
Glycomed (Ligand Pharmaceuticals)	GM6000 and analogs	MMPI	Research (5/98) USA
Ilex Oncology	THP-Dox	Angiogenesis inhibitors that also deliver doxorubicin to tumors ❑ injection	Preclin (6/98)➢USA
ImClone Systems		Antibodies against the KDR/FLK-1 tyrosine kinase receptor of VEGF expressed on tumor-associated capillary blood vessels; blocks *in vitro* binding of VEGF to the human KDR receptor and inhibits VEGF-stimulated growth endothelial cells	Preclin (3/98)➢USA ❑ solid tumors
Imutec Pharma ❑ Harvard U Medical School	Clotrimazole	Stops cells from multiplying by depleting them of calcium and halts cell proliferation at G1	Preclin (5/98)➢USA ❑ solid tumor
ImutecPharma (NuChem Pharmaceuticals) ❑ Harvard U Medical School, Torcan Chemical	NuChem	Clotrimazole analogs	Research (5/98)➢USA ❑ solid tumors
Ixsys	Vitaxin	Humanized derivative of the mouse LM609 MAb, constructed by CDR grafting, directed to integrin $\alpha v\beta 3$	Phase I (b4/97, o3/98)➢USA ❑ advanced solid tumors
Lane Labs-USA	BeneFin	Powdered shark cartilage extract ❑ PO	Phase II (b4/98)➢USA ❑ advanced primary intracranial and spinal axis tumors
Magainin Pharmaceuticals	Squalamine	Aminosterol; dogfish shark-derived peptide; cationic steroid characterized by a condensation of an anionic bile salt intermediate with the polyamine, spermidine ❑ IV	Phase I (o5/98)➢USA ❑ lung cancer
Merck KGaA		Angiogenesis inhibitor	Preclin (3/98)➢Germany ❑ solid tumors
National Cancer Institute (NCI)	Carboxyamidotriazole (CAI) ❑ NSC-609974	Synthetic signal transduction inhibitor that modulates non-voltage-gated calcium influx-regulated (non-excitable) signal pathways; metastasis inhibitor that targets a pertussin toxin-sensitive G protein; reversibly inhibits angiogenesis, tumor cell proliferation, and metastatic potential ❑ PO	Phase I (12/96)➢USA ❑ solid tumors; phase I (2/96)➢USA, (in combination) ❑ solid tumors, refractory lymphoma; preclin (11/96)➢USA ❑ glioma, high-grade astrocytoma; phase II (b12/97) ❑ androgen-independent prostate cancer
National Cancer Institute (NCI)	COL-3, NSC-683551	MMPI	
National Cancer Institute (NCI)		Human interferon-inducible protein 10 (IP-10), a chemokine, a secreted protein (MW=8.6 kD) that inhibits colony formation by bone marrow hematopoietic cells, exerts an antitumor effect, functions as a chemoattractant and is a potent inhibitor of angiogenesis	Research (7/98); available for licensing
NeXstar Pharmaceuticals		Aptamer antagonists of VEGF	Preclin (3/97)➢USA ❑ solid tumors, hematologic malignancies
NeXstar Pharmaceuticals		Platelet-derived growth factor (PDGF) aptamer antagonist	Preclin (4/97)➢USA
Novartis	CGS 27023A	Orally-available, broad spectrum MMPI	Phase I (o3/98) Europe ❑ solid tumors
OXiGENE ❑ Arizona State U	Combretastatin A-4	Naturally-occurring substance isolated from the South African tree *Combretastatin caffrum*	Preclin (97)➢USA ❑ solid tumors

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Parke-Davis ❑ U Texas MD Anderson Cancer Center, NIH	Suramin (SUR) ❑ CI-1003, NSC-34936 ❑ Moranyl	Polysulfonated naphthathylamine derivative; antiparasitic agent ❑ bolus, continuous IV	Phase II (2/97)➢USA ❑ ovarian cancer, refractory; phase III (b2/94)➢USA ❑ metastatic hormone-refractory prostate cancer; phase II (o2/98)➢USA ❑ progressive malignant glioma
Parke-Davis ❑ NCI	Suramin (SUR) ❑ NSC-34936, EUC-DON-9420, NCI-T94-0033O ❑ Moranyl	Polysulfonated napthylamine; non-specific cell killing agent; inhibits angiogenesis and enhances apoptosis	Phase III (b2/94)➢USA ❑ metastatic, hormone refractory prostate cancer; phase II (o2/98)➢USA ❑ adult recurrent or progressive malignant glioma
Peregrine Pharmaceuticals (Techniclone)		A vascular targeting agent (VTA) consisting of an antibody to the VEGF receptor as the targeting device linked to tissue factor CM, a protein which causes coagulation; intended to do focal damage to a blood vessel to cause its degeneration ❑ injection	Preclin (98)➢USA ❑ solid tumors
Pharmacia & Upjohn	Suradista ❑ FCE26644	New sulphonated distamycin A derivative blocking angiogenesis and neovascularization	Phase I (o3/98) Europe ❑ solid tumors
Progenitor ❑ Vanderbilt U		Small molecule or peptide inhibitors of developmentally-regulated endothelial cell locus (del-l) gene that is believed to be linked to angiogenesis	Research (2/98)➢USA ❑ solid tumors
Regeneron Pharmaceuticals ❑ Procter & Gamble	Angiopoietin-2 (Ang2)	Angiopoietins are a new family of ligands (and their receptors, the TIE family of receptors) that appear to regulate angiogenesis by activating or inhibiting these TIE (tyrosine kinase with immunoglobulin- and EGF-like domains) receptors; TIEs exist almost entirely on endothelial cells	Research (97)➢USA
Repligen	Glyceptor assay	High throughput binding assay; detects inhibitors of glycosaminoglycan binding basic fibroblast growth factor (bFGF) and VEGF	Research (98)➢USA
Repligen	RG8803	Small molecule inhibitor of bFGF and VEGF	Research (98)➢USA
Repligen ❑ Repligen Clinical Partners, New York U	Recombinant platelet factor-4 (rPF4)	Recombinant human protein ❑ intralesional, IV, subcutaneous	Phase II (9/96)➢USA ❑ Kaposi's sarcoma (KS), colon cancer, malignant melanoma, renal cell carcinoma
Ribozyme Pharmaceuticals (RPI) ❑ Chiron, U Colorado	RPI.4610	Chemically-synthesized, ribozyme-based therapeutic directed at the VEGF receptor FLT-1 mRNA	Preclin (4/98)➢USA ❑ solid tumors
Searle	SC-236	Cyclooxygenase-2 (COX-2) selective inhibitor; antiangiogenic	Preclin (3/98)➢USA ❑ solid tumors
Searle		Small molecule peptidomimetic antagonist of $\alpha v\beta 3$ a heterodimeric cell adhesion receptor of the integrin superfamily found on the surface of activated endothelial cells	Preclin (3/98)➢USA ❑ solid tumors
Selective Genetics (was Prizm Pharmaceuticals)		Fibroblast growth factor (FGF)-targeted adenoviral vector; angiogenesis inhibitor	Preclin (o5/98)➢USA ❑ ovarian cancer, pancreatic cancer
SmithKline Beecham	SB 220025	Antiangiogenic imidazole; selective inhibitor of p38 MAP kinase	Phase I (o5/98)➢USA ❑ solid tumors
Sugen	SU5416	Small molecule drug targeting the VEGF-mediated Flk-l tyrosine kinase (TK) pathway; blocks angiogenesis ❑ IV, PO	Phase I (o3/98)➢USA; phase I/II (b6/98)➢UK ❑ solid tumors (IV)
Taiho Pharmaceutical	TAS-102	Antitumor nucleoside with activity against primary tumors and metastases	Preclin (3/98)➢Japan ❑ solid tumors

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Takeda ❑ Harvard Medical School, TAP Pharmaceuticals, Dana-Farber Cancer Institute	Carbamic acid ❑ TNP-470 (formerly AGM-1470)	A fumagillin analog isolated from *Aspergillus fumigatus*; antiangiogenic and antibiotic compound ❑ IV	Phase III (1/97)➢USA ❑ solid tumors; phase II (o3/98)➢USA ❑ refractory renal cancer; phase I (o2/98)➢USA ❑ neuroblastoma, pediatric brain cancer; phase I (o2/98)➢USA ❑ lymphoma and acute leukemia
Texas Biotechnology (TBC)	TBC1635	Inhibitor of VEGF	Research (2/98)➢ ❑ solid tumors
Xoma ❑ New York U Medical Center	XMP300	Antiangiogenic peptides derived from biologically active recombinant bactericidal/ permeability-increasing (BPI) protein sequences	Research (9/97)➢USA

Source: NEW MEDICINE Oncology KnowledgeBASE (nm/OK), June 1998.

information as a brand new development and an imminent cancer cure. However, to date, none of the clinical trials have produced spectacular results, and despite promising preclinical trials, many hurdles remain:

- drugs must show effectiveness in humans at dose levels that are safe for long-term use
- therapy may become prohibitively costly if long term (chronic) therapy is required
- delivery methods may need to be devised for chronic administration

Thalidomide, a proven antiangiogenic agent in humans, under development by EntreMed (Rockville, MD), is one of the more interesting antiangiogenics in clinical trials. As of early 1998, a phase II clinical trial, was being conducted by Royal Marsden NHS Trust (London, UK), designed to investigate the efficacy of thalidomide in the treatment of solid tumors and to monitor concentrations of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) as biological markers associated with tumor angiogenesis. The study has enrolled 48 patients with advanced solid tumors (ovarian cancer=17, melanoma=16, renal carcinoma=8, and breast cancer=7) who were treated with thalidomide (100 mg) *nocte* until progression. Assessments made at 0, 1, 3 and 6 months included tumor imaging, symptom distress scale questionnaire, sensory nerve action potential amplitude and serum and urinary VEGF and bFGF concentrations. Three (6.2%) patients had a differential response, and disease stabilized in 10 (20.8) for up to 25 weeks (range=8-25 weeks, median=12 weeks). QoL data analysis shows an improvement in appetite and sleeping. Toxicities included lethargy and skin rash. Stable disease was associated with stable/falling serum and urinary VEGF concentrations and progressive disease with rising concentrations of VEGF. Serum bFGF was detected in only 4 patients, all of whom progressed rapidly (Eisen T, etal, ASCO98, Abs. 1699:441a).

In an NCI-sponsored 16-patient phase II clinical trial, reported in April 1998, at the National AIDS Malignancy conference in Bethesda, MD, among 13 evaluable patients with Kaposi's sarcoma (KS), there were six PR (46%) and the progression-free survival was 36 weeks. Toxicity associated with the treatment that resulted in the withdrawal of three patients, included fever, myositis and depression.

Endostatin and Angiostatin, two proteins isolated by researchers in the laboratory of Judah Folkman, MD, of Children's Hospital and Harvard Medical School (Boston, MA), are also being developed by EntreMed. When compared with cytotoxic agents in animal models, both Endostatin and the cytotoxics originally caused tumors to regress. But when tumors were allowed to grow back, cytotoxic agents lost their effectiveness, probably as a result of drug resistance, while Endostatin continued to shrink tumors for extended periods of time with no apparent toxicity. Also, drug resistance did not occur when Endostatin was repeatedly administered to mice (Boehm T, etal, Nature, 27 Nov 1997, 390:404-7). Results from murine studies also suggest that these antiangiogenic compounds may be potent anticancer agents when used in combination with cytotoxic drugs. In animal models of various human cancers, these compounds prevented metastases after surgical removal of tumors known for their metastatic potential and potentiated tumor kill when combined with various cytotoxic agents.

In June 1998 EntreMed announced that the crystal structure of Endostatin was revealed by Dr. Bjorn R. Olsen, of Harvard Medical School and a team of crystallographers from the UK and Germany (Hohenester E, etal, Embo J, 16 Mar 1998, 17(6):1656-64). EntreMed signed a sponsored research agreement with Harvard Medical School to fund Dr. Olsen's research until 2001. Complementing the work of EntreMed's key collaborator, Dr. Folkman, Dr. Olsen and his colleagues will continue to examine the mechanisms that allow Endostatin to inhibit growth of endothelial cells necessary for formation of new blood vessels. With the crystal structure of Endostatin completely defined, it would be possible to characterize specific mechanisms in detail, enabling the design of molecular analogs with potentially greater biological activity.

Currently, Endostatin is efficiently produced by genetic engineering methods and the Endostatin-generating yeast is now being grown in pilot-scale fermenters in preparation for preclinical and GMP production for human clinical trials. The genetically-engineered version of Endostatin protein caused nearly complete suppression of tumor-induced angiogenesis and tumor growth in both mouse cancers and human cancers, when grown in mice. NCI has made it a high priority to move research forward on Endostatin and related compounds, so that clinical trials in humans may begin sometime in 1999, and is working with EntreMed on production issues for Endostatin and with Bristol-Myers Squibb, for Angiostatin. It is expected that these compounds will be tested separately for safety and efficacy in humans before they can be tested in combination.

An interesting approach devised by scientists at Genetix Pharmaceuticals (Cambridge, MA), in collaboration with Dr. Folkman's group as well as Centre Léon Bérard (Lyon, France), centers on a gene therapy strategy to achieve high sustained systemic levels of Angiostatin and Endostatin *in vivo*, following bone marrow transplantation with retrovirally transduced cells (Pawliuk R, etal, AACR98, Abs. 3772:555). Bone marrow stem cells, genetically modified *ex vivo* to secrete antiangiogenic proteins into the bloodstream, were transplanted in the bone marrow of mice. Twelve weeks hence, the mice showed high, systemic levels of blood cells containing the marker proteins. Also, when these mice were subsequently injected under the skin with melanoma cells, tumor growth was suppressed (Bachelot T, etal, AACR98, Abs. 1856:271-2). Although it was shown in the past that tumor cells may be genetically-modified to secrete antiangiogenic proteins, in this approach normal stem cells are transduced with the genes encoding these proteins to potentially empower the body to produce its own proteins and obviate the requirement of daily injections to maintain sufficient levels of these proteins to sustain tumor regression.

Squalamine, another angiogenic, under development by Magainin Pharmaceuticals (Plymouth Meeting, PA) is in phase I clinical trials in lung cancer. In animals models squalamine decreased lung metastases by 50% compared to controls when administered alone and, when administered with cyclophosphamide, it delayed tumor growth 2.1-2.6-fold compared with cyclophosphamide alone, and decreased the mean number of lung metastases per animal to 0.5-1 compared to 30 in controls. Also, Squalamine, in combination with cisplatin or 5-FU, delayed tumor growth 3.5-3.8-fold and 1.8-2.4-fold, respectively, and decreased lung metastases relative to cisplatin or 5-FU alone. Similar tumor growth delays were seen in rats bearing the non-metastatic 13762 mammary carcinoma, when squalamine was combined with cyclophosphamide or cisplatin. Squalamine alone also increased oxygenation of the 13762 tumor, increasing the median pO_2 from 3.2 to 9.2 mm Hg (William JI, etal, AACR98, Abs. 2135:312).

CHEMOPREVENTION

Cancer prevention remains an elusive goal. Ideally, it would be most desirable if a non-pharmacologic prevention approach is identified that would carry minimal risk. However, most clinical trials involving dietary supplements and/or vitamins have not produced definitive results. Prevention by vitamin supplementation is a very attractive means of reducing cancer risk because vitamins are generally not associated with serious side effects when ingested on a chronic basis. Recently, results from The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, a placebo controlled clinical trial involving 29,133 male smokers aged 50-69 years, conducted in Finland, showed that supplementation with vitamin E (α-tocopherol) reduced prostate cancer incidence by 32% and deaths attributed to this cancer by 41%. In contrast, ingestion of vitamin A (β-carotene) appeared to increase incidence of prostate cancer by 23% and deaths by 15%. However, trials involving pharmacologic approaches appear to have been more productive albeit it often seems that with these agents prevention of one disease may give rise to other health problems.

Antiestrogens in Breast Cancer

The dilemma arising from use of pharmacologic agents for chemoprevention is best illustrated by the case of antiestrogens in the prevention of breast cancer. Much has been made of the preliminary results of a placebo-controlled, double-blind, randomized clinical trial, conducted by the National Surgical Breast and Bowel Project (NSABP), that found a 45% reduction in breast cancer incidence. This study, carried out between April 1992 and September 1997 in over 300 centers in North America, enrolled 13,388 women at high risk of breast cancer who were treated either with tamoxifen or placebo. Under the study protocol, women over the age of 35 (about 40% were ages 35 to 49, 30% were 50 to 59, and 30% were 60 or older; about 3% of the participants were minorities), considered at risk for breast cancer ("high risk" determined by looking at each woman's family history of breast cancer, age, pregnancy history, and age at time of menstruation, among other factors), were randomly assigned to tamoxifen (Nolvadex; Zeneca), at two 10 mg pills daily, or to a placebo.

The study was designed to assess the efficacy and safety of tamoxifen as a possible drug for the prevention of breast cancer. With an average follow-up of 3.6 years, 85 women on tamoxifen developed breast cancer compared to 154 cases on placebo, a 45% reduction in disease incidence. The effect was seen in all age groups; it was 35.6% (59 versus 38) in younger patients (35-49 years-of-age), 47.8 (45 versus 24) in those 50-59 years-of-age but was most pronounced at 53.1% in those over 60 years-of-age. Eight women died of breast cancer, three in the tamoxifen group and five in the placebo group. The study also demonstrated a 52% reduction in the rate of non-invasive breast cancer (31 versus 59 women) and a 35% lower risk of frac-

tures of the hip, spine, and wrist. On the other side of the coin, in women over 50, there was a two-fold increased risk of developing endometrial cancer (33 on tamoxifen versus 14 on placebo), an increased risk of pulmonary embolism (17 on tamoxifen versus 6 on placebo), and an increased risk of thrombosis (30 on tamoxifen versus 19 on placebo). Women under 50, however, did not experience any excess risk of side effects (Cronin W, etal, Special Presentation at Plenary Session, ASCO98, Abs. 3A).

Tamoxifen has been shown to be effective in preventing recurrence of breast cancer (see accompanying article on page 823) and, in this case, its benefit is undeniable. However, despite the glowing reports regarding its role in preventing breast cancer in healthy women at high risk for developing this disease, its side effect profile is quite disturbing. Along with the 45% reduction in the incidence of breast cancer, there was 57.6% rise in the incidence of endometrial cancer, 64.7% of pulmonary embolism (PE) and 36.7% of deep vein thrombosis (DVT). Two women in the tamoxifen group died from PE. These findings are despite the fact that women at increased risk for blood clots could not participate in the study. Based on these statistics, if the 29 million American women considered high risk for breast cancer are treated with tamoxifen, the benefits must be weighed against the drawbacks of this treatment:

	Annual Incidence with Tamoxifen (#)	Annual Incidence without Tamoxifen (#)
Breast Cancer	87,000	145,000
Endometrial Cancer	39,100	13,533
Pulmonary Embolism	16,433	5,800
Deep Vein Thrombosis	29,000	18,366
Total	171,533	182,699

Two important considerations must be kept in mind when looking at these statistics:

- Women who were administered the drug were healthy to begin with. Administering healthy subjects drugs that may prevent one devastating disease but increase the risk of contracting another, is a rather imperfect approach to public health. Chronic treatment with any drug is risky and must only be undertaken under the most extreme situations. The recent findings regarding prophylactic use of tamoxifen leave women where they stood before, i.e. they are being asked to choose between possibly avoiding breast cancer but at a risk of potentially contracting endometrial cancer, or developing dangerous complications such as PE or DVT. Basically the choice is between two evils and the chance of getting any disease at all if one does nothing is probably as good as anything offered by this treatment. The reports on tamoxifen's role as a breast cancer chemopreventive were simply not very meaningful, in general, and will probably do little to help any healthy woman considered at high-risk for breast cancer, in particular.
- The glowing positive reports regarding the outcome of this trial failed to address many very critical points regarding the long-term effects of this treatment. What is the relationship between duration of therapy and cancer prevention? How long should women take this drug? Does the risk return when the drug is discontinued? Does the effect diminish after a certain period? Should healthy younger women take this drug for the rest of their lives? Do the drug's circulatory side effects increase with chronic use? What was the estrogen receptor status of the detected cancers in either group?

The challenge in conducting chemoprevention studies is illustrated by their costs and their long duration. However, although this trial was projected to cost $70 million, the total cost is estimated at $50 million, including $10 million for two more years of follow-up. All expenses were paid by the NCI with the exception of $3.5 million contributed by the National Heart, Lung, and Blood Institute (NHLBI); tamoxifen was provided free of charge by Zeneca.

Raloxifene (Evista; Eli Lilly), a novel selective estrogen receptor modulator (SERM) approved and launched in the USA in February 1998 for prevention of osteoporosis, was also found to substantially reduce risk of cancer in healthy postmenopausal women. A new study indicates that daily use of raloxifene lowers the risk of breast cancer by 66% in postmenopausal women with normal risks for the disease, also reducing the risk of ER+ breast cancer by 87%; it has no affect in ER- breast cancer. In a two-year study, 7,705 postmenopausal women being treated for osteoporosis, and who had no history of breast or endometrial cancer, were randomized to raloxifene (60 mg or 120 mg) daily or placebo, in a ratio of two to one. At a median 28.9 months of follow-up, breast cancer was confirmed in 32 women, 11 (0.21%) in the raloxifene group and 21 (0.82%) of the placebo group. In addition, there appeared to be no statistically significant increase in the risk of endometrial cancer, and, in fact, there was a slight reduction in this risk. Raloxifene did increase a woman's risk of developing blood clots, but this adverse effect is seen with other hormonal approaches, as well. Longer-term effects of raloxifene are presently under study (Cummings SR, etal, ASCO98, Abs. 3:2a). If, indeed, Evista does not carry the endometrial cancer risk, the fact that it may combine prevention of osteoporosis and breast cancer may boost its sales that have had a slow start in 1998. A large randomized clinical trial, the Study of Tamoxifen and Raloxifene (STAR), comparing tamoxifen to raloxifene, to enroll 22,000 post-menopausal women, is expected to begin in the fall of 1998.

Other selective estrogen receptor modulators in clinical trials include SmithKline Beecham's idoxifene, also in clinical evaluation for the prevention of both osteoporosis and breast cancer, Eli Lilly's SERM III, a raloxifene analog,

and Pfizer's droloxifene. Droloxifene development in the treatment of advanced breast was discontinued but it is being evaluated as a chemoprevention option. Another SERM, GW5638, under development by Glaxo Wellcome, is being evaluated in preclinical trials. A pure antiestrogen, EM-800, is also in development by Endorecherche (Quebec, Canada). As additional information regarding the mechanisms of antiestrogen activity is being elucidated, third generation agents may provide more effective and safer chemoprevention agents.

Next issue: *Genomics and gene transfer/therapy; immunotherapy/vaccines; classical resistance modulation; drug delivery; clinical trials in oncology; competition in the oncology sector; etc.*

MEETING COVERAGE

ADVANCES IN THE TREATMENT OF BREAST CANCER

FROM THE 34TH ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY LOS ANGELES, CA; MAY 16-19, 1998

ANTIESTROGENS IN THE PREVENTION OF RECURRENCE OF EARLY BREAST CANCER

Considerable positive news were recently released regarding the use of antiestrogens in preventing breast cancer in high-risk women (see accompanying article, p 821-823) and in recurrence prophylaxis. Although the concept of treating healthy, high-risk women with antiestrogens remains controversial, the situation is much more clear-cut when antiestrogens are used to prevent breast cancer recurrence. An analysis of data from 37,000 women with early-stage breast cancer (Stage I and II) from 55 randomized trials of tamoxifen, beginning before 1990, showed that tamoxifen provides a clear benefit for women with estrogen receptor-positive (ER+) breast cancer. Among those treated with tamoxifen, there were 47% fewer recurrences and 26% fewer deaths. Also, women taking tamoxifen experienced 47% fewer new breast cancers in the opposite breast compared to controls. This analysis, however, did not show benefit in women with ER- breast cancer and use of tamoxifen to treat these women remains to be established by further research.

This analysis also confirmed that 5-year treatment of ER+ breast tumors with tamoxifen is equally beneficial in premenopausal and postmenopausal women. It is also noteworthy that the survival advantage for women treated with tamoxifen increased for up to at least 10 years, even though treatment lasted only 5 years as recommended by NCI guidelines that limit use of tamoxifen in the treatment of breast cancers, outside of clinical trials, to five years.

This analysis also demonstrates conclusively that, despite the fact that tamoxifen increases the risk of endometrial cancer two to three times above that in the general population, and doubles the chance of pulmonary embolism, for women with ER+ breast cancer, its benefits in preventing disease recurrence and death from breast cancer far outweigh its risks. Therefore, adjuvant treatment with tamoxifen, with or without additional chemotherapy, should be carefully considered for all women with ER+ breast cancer (Early Breast Cancer Trialists' Collaborative Group, Lancet, May 1998; 351:1451-67).

Expression of c-erbB-2 and Antiestrogen Therapy

Expression of c-erbB-2 in breast cancer patients may be a prediction of chemosponsiveness. In a 14-year follow-up of 433 Italian women who had enrolled in the GUN trial from February 1978 to December 1983, adjuvant tamoxifen was found to reduce relapse and death rates in breast cancer independently of nodal and menopausal status. The women were randomized either to tamoxifen (n=206) for 2 years or to no hormonal therapy (n=227), and all premenopausal node-positive women were also treated with 9 cycles of cyclophosphamide, methotrexate, and 5-FU (CMF), prior to hormonal therapy. Interestingly, tamoxifen improved disease-free and overall survival only in c-erbB-2-negative patients, while showing a paradoxical detrimental effect in c-erbB-2-positive patients. A multivariate analysis, taking into account lymph node status, menopausal status, nuclear grade, and ER status, confirmed the predictive value of c-erbB-2 expression (Bianco AR, etal, ASCO98, Abs. 373:97a).

In a similar study, c-erbB-2 was prospectively measured in 595 (of 1,470) ER+, node-positive, postmenopausal patients participating in Intergroup Trial 0100, which showed that the combination of CAF chemotherapy consisting of cyclophosphamide, doxorubicin and 5-fluorouracil (5-FU), and tamoxifen to be superior to tamoxifen alone, particularly in c-erbB-2-positive patients. Disease-free survival at 4 years was superior in women with c-erbB-2 expression treated with the CAF and tamoxifen combination (74% versus 41% and 75% versus 56% using two different MAbs to measure c-erbB-2 expression) compared to those treated with tamoxifen alone. Unfortunately, this study had a low statistical power to answer predictive questions because of the short follow-up, a 10:3 randomization of CAF + tamoxifen versus tamoxifen alone, and a 16% rate of overexpression of c-erbB-2. Also, within smaller subsets critical to the interpretation of this study, there were imbalances between other important variables that prevented a straightforward correlation. More information is being collected and additional cases are being analyzed, to better understand the role of c-erbB-2 as a prognostic factor (Ravdin PM, etal, ASCO98, Abs. 374:97a).

TREATMENT OF LOCOREGIONAL DISEASE

Treatment using breast-conserving surgery and locoregional radiation (LRRT) therapy was shown to be as effective as mastectomy in women with Stage I or II breast cancer.

Also, radiation therapy, after surgery of any type, was found to be beneficial in terms of a survival benefit and is often recommended for patients at high risk for locoregional recurrence after mastectomy. Between 1977 and 1992, 221 such patients were treated with radiation therapy, with or without adjuvant systemic chemotherapy. The reasons for the high-risk classification was T3 or T4 tumors (14%), positive lymph nodes (29%), close or positive margins at resection (15%), or multiple risk factors (39%), although 3% may not have met current criteria for radiation therapy. Radiation therapy consisted of 45-50.4 Gy to the chest wall in 1.8-2.0 Gy fractions. Regional lymph nodes were treated in 187 patients (85%) and 151 (68%) were treated with adjuvant CMF (n=73), CAF (n=73), or other chemotherapy regimens (n=5). Patients treated with chemotherapy were younger (median age=48 versus 64 years) and had more positive lymph nodes (median=5 versus 1). Adjuvant hormonal therapy was used in 116 patients (53%).

At a median follow up of 4.3 years, the actuarial 10-year locoregional failure rate was 11%. The first site of failure was distant metastases in 75 patients (34%), locoregional recurrence in 11 patients (5%) and in both sites in 3 patients (1%); 60% had no evidence of disease at last follow up. Of those with locoregional recurrence as first sign of failure, 9 (82%) subsequently developed metastatic disease. The median time to locoregional first failure was 1.3 years. The median time to distant metastases after locoregional first failure was 0.3 years. Only 40% of patients treated with chemotherapy were free from distant metastasis compared to 63%, and overall survival at 10 years was lower in this group (65% versus 82%); however, there was no difference in locoregional first failure (7% versus 8%). This group had a worse outcome because of poor prognostic factors. According to this study, postmastectomy radiation therapy is associated with an 89% rate of locoregional control in a high risk population and patients who develop locoregional recurrence after radiation therapy are at a very high-risk of developing metastatic disease. Radiation therapy after mastectomy is recommended to optimize locoregional control for high-risk breast cancer patients (Metz JM, etal, ASCO98, Abs. 462:121a).

Recently published data also show that LRRT augments survival benefits of adjuvant chemotherapy, following mastectomy, in premenopausal women. In a randomized clinical trial conducted in Denmark, 1,708 women who had undergone mastectomy for pathological Stage II or III breast cancer, were randomly assigned to either 8 cycles of adjuvant CMF, plus irradiation of the chest wall and regional lymph nodes (n=852), or 9 cycles of CMF alone (n=856). Median follow-up was 114 months. Endpoints were locoregional recurrence, distant metastases, and disease-free and overall survival. The frequency of locoregional recurrence alone, or with distant metastases, was 9% among women treated with radiotherapy plus CMF, and 32% among controls; the probability of survival free of disease after 10 years was 48% and 34%, respectively, and overall survival at 10 years was 54% and 45%, respectively. Multivariate analysis demonstrated that irradiation after mastectomy significantly improved both disease-free and overall survival, irrespective of tumor size, number of positive nodes, or histopathologic grade (Overgaard M, etal, NEJM, 2 Oct 1997, 337(14):949-55). Preliminary data also indicate that LRRT improves survival of postmenopausal women.

Use of Breast Conserving Therapy in the USA

Thousands of women every year could be spared mastectomies if national guidelines developed six years ago were properly followed. Based on NCI guidelines, approximately 75% of women diagnosed with early-stage breast cancer are eligible for breast-conserving therapy (BCT), which consists of lumpectomy followed by radiation therapy. According to those guidelines, age, prognosis, and tumor type should not be used to chose mastectomy over BCT and only large tumor size, small breast size in comparison to tumor size, early pregnancy, and multiple tumors in various sites of the breast, should be used as indications for mastectomy. In an effort to determine current patterns of care and to evaluate adherence to guidelines, a study analyzed the treatment of 17,931 women with Stage I and II breast cancer at 827 different hospitals across the USA. Only 44.1% (7,914) of patients underwent BCT. Furthermore, for every decade increase in age, from 60 years upwards, there was a decrease in the use of BCT, although guidelines stress that age should not be a selection factor. In addition, the study found that only 78% of BCT patients were treated with radiation therapy, again contrary to practice guidelines, largely because of failure to refer patients for radiation. Looking at subgroups, women on Medicaid or Medicare were more likely to undergo a mastectomy compared to those in an HMO or with private insurance. In addition, there was more breast preservation in the Northeast and on the West Coast, with more mastectomies being carried out in the South and the Midwest. It would appear that doctors still believe that if the patient has "bad" (bigger tumor size, lymph involvement) breast cancer, there is a need to remove the breast, even though this has been shown not to be true (Morrow M, etal, ASCO98, Abs. 379:986).

Economics of Locoregional Radiotherapy in Canada

Possible clinical and economic implications of LRRT for Stage II node-positive breast cancer were evaluated using the breast cancer module of Statistics Canada's POpulation HEalth Model (POHEM). According to cancer registry data, 39% of women with Stage II disease undergo BCT followed by radiotherapy at an average cost of CDN$12,340 whereas <8% have mastectomy followed by radiotherapy at an average cost of CDN$11,530. Preliminary results indicate that mastectomy plus LRRT for node-positive breast cancer would cost $12,650 compared to $7,680 for mastectomy alone, but would provide a 10-year survival gain of 9%, similar to that obtained with BCT followed by radiotherapy (Verma S, etal, ASCO98, Abs. 464:121a).

ADJUVANT CHEMOTHERAPY

CAF versus CMF

In a comparison of the CAF and CMF regimens as adjuvant chemotherapy to prevent recurrence of breast cancer after surgery, CAF resulted in a statistically significant higher survival rate in women with localized breast cancer at a high risk of recurrence. Furthermore, the study demonstrated the benefit of adding tamoxifen to chemotherapy in ER+ patients. In this clinical trial, 2,691 high-risk patients were randomized to CMF or CAF, with or without tamoxifen, for five years, and 1,208 low-risk patients were followed without adjuvant therapy. Results show that CAF is slightly superior to CMF, with 5-year relapse-free rates of 86% versus 84%. Chemotherapy plus tamoxifen were additive, with particular benefit in ER+ women in whom overall five-year relapse-free survival rates were 93% versus 91%. A subset of low-risk patients, based on tumor size, receptor status, and 5-phase fraction, did very well without adjuvant treatment (Hutchins L, etal, ASCO98, Abs. 2:2a).

Capecitabine

Home-based monotherapy with capecitabine was shown to be comparable in efficacy to CMF combination therapy, as first-line chemotherapy of breast cancer in women >55 years of age. In a phase II clinical trial, 95 women with breast cancer were randomly assigned to capecitabine (2510 mg/m^2) administered daily in two doses, on days one to 14 of each three-week cycle, or CMF, administered IV on day one, every 21 to 28 days. Sixty-two patients were treated with capecitabine and 33 with CMF. In 61 evaluable patients on capecitabine there were 15 objective responses (24.6%) compared to five responses (16%) in 32 evaluable women on CMF. Median times to progression were 1,332 days in the capecitabine group versus 94 days in the CMF-treated women. Grade 3/4 adverse effects on capecitabine were hand-foot syndrome (16% versus 0% on CMF) and diarrhea (8% versus 3%). Dose reduction or treatment interruption adequately controlled these toxicities. In contrast, incidence of Grade 3/4 hematologic toxicity was higher in the CMF group (47% versus 20%) (O'Shaughnessy J, etal, ASCO98, Abs. 398:103a).

Paclitaxel

Paclitaxel, added to standard adjuvant chemotherapy with doxorubicin and cyclophosphamide in women with node-positive primary breast cancer, significantly increases survival. In a phase III clinical trial, 3,170 women with primary breast cancer involving the axillary lymph nodes, were randomized in a 3 x 2 factorial trial, to be treated either with cyclophosphamide (600 mg/m^2), doxorubicin (60, 75, or 90 mg/m^2), and G-CSF, every three weeks, for 4 cycles, followed either by no paclitaxel or by paclitaxel (175 mg/m^2), every three weeks, for four cycles. A five-year regimen of daily oral tamoxifen (20 mg) was offered to ER+ women. At 18 months follow-up, 97% of women treated with adjuvant therapy that included paclitaxel were alive, compared to 95% of those treated with standard adjuvant therapy alone, and 90% were relapse-free versus 86%. While benefits seem small at this juncture, no differences were expected so early in this type of study, with benefits possibly growing larger with long-term follow-up (Henderson IC, etal, ASCO98, Abs. 390A:101a).

A combination of paclitaxel and anthracylines was evaluated as first-line chemotherapy in three phase I/II clinical trials conducted in Italy, involving 148 women with advanced breast cancer. Treatment regimens consisted of either:

- epirubicin (90 mg/m^2) plus paclitaxel (200 mg/m^2), administered as a 3-hour infusion on day 1, every 21 days (n=80 and 70% were pretreated with adjuvant chemotherapy)
- doxorubicin (50 mg/m^2) administered 16 hours before paclitaxel, every 21 days (n=32 and 41% were pretreated)
- doxorubicin plus paclitaxel on day 1, every 21 days (n=36 and 56% were pretreated).

All regimens showed very high activity with an overall response rate of 78%-84% and a CR of 19%-31%. Nearly 20% of those responding achieved a response after more than 4 treatment cycles. Toxicities were manageable. Clinical cardiotoxicity during treatment, reversible with therapy, was observed in 5%, 0% and 6% of patients in the three regimens, respectively. Delayed Grade 3 cardiotoxicity (median time of observation=12 months), was observed in one patient being treated with the first regimen. However, despite the high response rate, the progression-free survival ranged only from 10-12 months, similar to the 10 months achieved with CEF consisting of cyclophosphamide, epirubicin and 5-FU.

Because patients responded late in the treatment, it was hypothesized that a more prolonged paclitaxel regimen would improve the outcome of the high percentage of responding patients. Therefore, a phase III multicenter clinical trial was undertaken to evaluate differences in progression-free survival and overall survival between maintenance chemotherapy with paclitaxel versus no maintenance. After achieving an objective response or disease stabilization with one of the three reported regimens, patients are being randomized to either paclitaxel (175 mg/m^2), every 3 weeks, for 8 cycles, or to control. The study will enroll 400 patients (Del Mastro L, etal, ASCO98, Abs. 523:137a).

TREATMENT OF METASTATIC BREAST CANCER

Docetaxel

A two-year outcome analysis of patients with advanced, breast cancer treated with docetaxel in a community setting, pointed out that women who responded to treatment with docetaxel survived significantly longer compared to non-responders. In this study, patients with locally-advanced or metastatic breast cancer who had relapsed or failed to respond to previous chemotherapy, were treated

with docetaxel (100 mg/m^2) as a one-hour IV infusion, every three weeks. Overall, 442 women were enrolled, and 377 were treated with at least one course of docetaxel (91% were already treated with one prior anthracycline-based regimen). Among 331 patients treated with at least one docetaxel course, the overall response rate was 45.6%, with 18 CR (5.4%) and 133 PR (40.2%). In addition, disease stabilized in 131 (39.6%). The two-year MST was 194 days for all treated patients and 312 days for the 151 responders (CR + PR); median survival was 358 days for those who experienced CR and 54 days for non-responders. Responders had a 41% one-year and 13% two-year survival rate, while 7% of all patients (26/377) were still alive at two years (Leonard RC, etal, ASCO98, 434:112a).

Paclitaxel

Higher doses of paclitaxel are not necessarily more effective in women with advanced breast cancer, so patients can be spared the higher toxicities associated with these high-dose regimens. In this study, 470 women with metastatic breast cancer were randomly assigned to paclitaxel at three different doses, 175 mg/m^2 (low), 210 mg/m^2 (medium), or 250 mg/m^2 (high), as a 3-hour IV infusion, every three weeks. Three-quarters of these patients were previously treated with chemotherapy for metastatic disease and the remaining were chemotherapy-naive. Higher-than-standard doses of paclitaxel did not improve survival, with MST being similar across the three treatment arms (9.8 months at 175 mg/m^2, 11.8 months at 210 mg/m^2, and 11.9 months at 250 mg/m^2). Furthermore, the drug's efficacy actually declined at higher doses, providing a 26% response rate at moderate dosing versus 23% at the highest dose. Time to disease progression, however, was improved at higher doses (3.8 months, 4.1 months, and 4.8 months respectively) but this small improvement is gained at increased drug toxicity (Winer E, etal, ASCO98, Abs. 388: 101a).

Also, administration of paclitaxel over a long period does not appear particularly beneficial. Because, in preclinical evaluations, prolonged paclitaxel infusion retarded or reversed anthracycline-resistance in metastatic breast cancer, it has been hypothesized that the antineoplastic activity of paclitaxel is schedule-dependent and that a 96-hour continuous infusion would exhibit more antineoplastic activity than the standard 3-hour approach. However in a multicenter randomized phase III clinical trial, paclitaxel, at a dose of 250 mg/m^2 as 3-hour infusion (n=88), repeated every 21 days, resulted in 3% CR, 20% PR and 18% MR and at a dose of 140 mg/m^2 as a 96-hour infusion (n=91), in 2% CR, 27% PR and 19% MR. MST was 11 months versus 10 months. Therefore, the long duration regimen did not confer any therapeutic advantage to justify the extra logistical support (Holmes FA, etal, ASCO98, Abs. 426:110a).

Vinorelbine and Paclitaxel Combination

The combination of vinorelbine and paclitaxel, administered as a continuous 96-hour infusion, has a low toxicity profile but significant antitumor activity in women with advanced breast cancer who have undergone prior chemotherapy, making this approach suitable as salvage chemotherapy. In a phase I/II clinical trial, 18 women were randomly assigned to six different doses of paclitaxel (50, 65, 80, 95, 110, 120 mg/m^2) as a 96-hour continuous infusion, in combination with a fixed dose of vinorelbine (12.5 mg/m^2), on days one and five, every three weeks. Another 24 patients were assigned to paclitaxel at three dose levels (110, 100, 90 mg/m^2) as a 96-hour continuous infusion, and a higher dose (15 mg/m^2) of vinorelbine, on days one and five, every three weeks. The suggested maximum tolerated doses of paclitaxel in the two schedules was 110 mg/m^2 and 90 mg/m^2, and of vinorelbine 12.5 mg/m^2 or 15 mg/m^2, respectively.

Among 37 evaluable women, 35 of whom had been previously treated with an anthracycline-containing regimen, there was an overall objective response rate of 46% (17 patients), with 5 CR (14%) and 12 PR (32%); disease stabilized in 14 patients (38%), and progressed in six (16%). Median duration of response was 27 weeks (4-49), median time to progression was 20 weeks (0-49+), and MST was 67 weeks (0-85+). With regard to the safety profile of the combination, toxicities were Grade 4 neutropenia (3%) and Grade 2/3 stomatitis (1.6%). There were no neurological and/or muscular toxicities, and no other major toxicities. In addition to being effective with low toxicity, this approach had several ancillary advantages. As no anthracycline was included, there was no risk of cardiac toxicity. The combination was cost-effective because only about 50% of the usual dosage of both agents was used. There was no need for premedication with steroids and, finally, alopecia requiring a wig was not universal in this patient population (Cocconi G, etal, ASCO98, Abs. 800:208a).

Losoxantrone

Losoxantrone, an investigational anthrapyrazole under development by DuPont Pharmaceuticals with structural similarities to both doxorubicin and mitoxantrone, when combined with paclitaxel, appears to be more effective than paclitaxel alone for the treatment of metastatic breast cancer, providing better response rates and longer progression-free survival. In a phase III clinical trial, patients with metastatic breast cancer were randomly assigned in a 2 to 1 fashion to either losoxantrone (50 mg/m^2) plus paclitaxel (175 mg/m^2), as a 3-hour IV infusion, or paclitaxel (175 mg/m^2) alone, as a 3-hour IV infusion. All women on combination therapy were also treated with G-CSF, while only those with hematologic toxicity in the paclitaxel alone group were administered G-CSF. Among 148 evaluable women, the objective response rate was 54% on losoxantrone plus paclitaxel, compared to 15% on paclitaxel alone. Furthermore, median progression-free survival was 230 days in the combination group versus 111 days for those on paclitaxel monotherapy. Grade 3/4 neutropenia was greater on combination therapy (66%) compared to paclitaxel monotherapy (32%) and Grade 3/4 thrombocy-

topenia was observed in 11% of those treated with the combination regimen (Kaufman PA, etal, ASCO98, Abs. 475:124a).

High-dose Chemotherapy/Stem Cell Transplantation (HCSCT) Compared with Chemotherapy Alone

In order to ascertain if there is a disease-free and overall survival benefit for high-dose chemotherapy/stem cell transplantation (HCSCT) as compared with chemotherapy alone in patients with metastatic breast cancer, a group of 144 women who were treated with HCSCT between 1991 and 1995, was compared with 135 carefully selected historical controls who were treated by chemotherapy alone. Median overall survival was 25.7 months with chemotherapy versus 28.1 months with HDSCT, and median progression-free survival was 9 months and 17.5 months, respectively. Use of multivariate analysis to adjust for baseline and therapy-related prognostic differences between groups, revealed a statistically significant difference in favor of HDSCT for both overall survival and progression-free survival. Use of HDSCT in metastatic breast cancer may have survival benefits independent of the effects of selection bias and variously cited prognostic factors. The magnitude of any benefit, if demonstrated in ongoing randomized trials, will have to be considered in context of increased costs/toxicity associated with transplantation, and potential differences in quality of life between the two therapeutic modalities (Bociek G, etal, ASCO98, Abs. 440:114a).

According to a formal retrospective cost analysis of high-dose chemotherapy with autologous stem cell transplantation (HCASCT) as compared with chemotherapy, undertaken in 1995 among 25 patients treated with chemotherapy and 13 treated with HCASCT by the Ottawa Regional Cancer Centre (ORCC)/University of Ottawa Bone Marrow Transplant Programme, the chemotherapy group used significantly more hormonal therapy, clinic/home nursing, and chemotherapy, whereas those treated wiyh HCASCT used significantly greater hospital resources. Mean cost of care over 12 months was CDN$22,764.31 for chemotherapy and CDN$36,341.46 for HCASCT. Mean cost of transplantation was CDN$23,415.76. The difference in cost remained similar when the analysis was limited to uncomplicated cases (Bordeleau L, etal, ASCO98, Abs. 415:108a).

Gemcitabine and Cisplatin Combination

Based on favorable *in vitro* results and encouraging pilot clinical trial experience, the combination of gemcitabine and cisplatin was evaluated in a phase II clinical trial designed to test its effects in heavily pretreated patients with metastatic breast cancer. Among 18 patients treated with cisplatin (30 mg/m^2) and gemcitabine (750 mg/m^2) on days 1, 8 and 15, every 28 days, there were 8 PR (44%), disease stabilized in 8 (44%) and progressed in 2 (11%). Response duration ranged from 7-21 months. Hematologic toxicity predominated and mild dysethesias and moderate alopecia were observed, but there were no treatment related deaths in 119 weekly treatments (Nagourney RA, etal, ASCO98, Abs. 619:161a).

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