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THE UNIVERSITY OF TEXAS SYSTEM CANCER CENTER  
M. D. ANDERSON HOSPITAL AND TUMOR INSTITUTE

Volume 28, Number 4

## Implant Relieves Chronic Pain, Delivers Drug Directly to Central Nervous System

The Ommaya reservoir, a device surgically implanted in the head to deliver morphine directly to the central nervous system, has provided pain relief for 26 cancer patients to date at UT MDAH. In contrast to oral and parenteral methods of drug administration, the Ommaya reservoir method requires small doses of morphine, thus causing few side effects.

According to C. Stratton Hill, MD, Department of Internal Medicine, director of the Pain Clinic, the reservoir had been used solely as a chemotherapy tool until about 3 years ago. At this time, a study at UT MDAH proved the reservoir also useful in relieving chronic pain in patients with tissue damage from tumors. The study, involving 6 patients, found that morphine administered by means of the reservoir, intrathecally through the lower back or intraventricularly through the right frontal region of the head, was highly effective. A small dose (2.5 mg to 4.0 mg) of specially processed, preservative-free morphine gave 80% to 100% pain relief within an hour of the injection. Relief continued for up to 24 hours without signs of lethargy or sedation.

Since 1980, Dr. Hill and his associates have successfully used the Ommaya reservoir in 20 patients. This experience has revealed more about the workings of the reservoir and the type of patient most likely to benefit from the device.

The Ommaya reservoir provides direct access to the central nervous system; this is the key to the reservoir's success. Any narcotic administered by standard methods must cross the blood-brain barrier to reach the central nervous system and cerebrospinal fluid, which saturates opiate receptor sites in the brain and

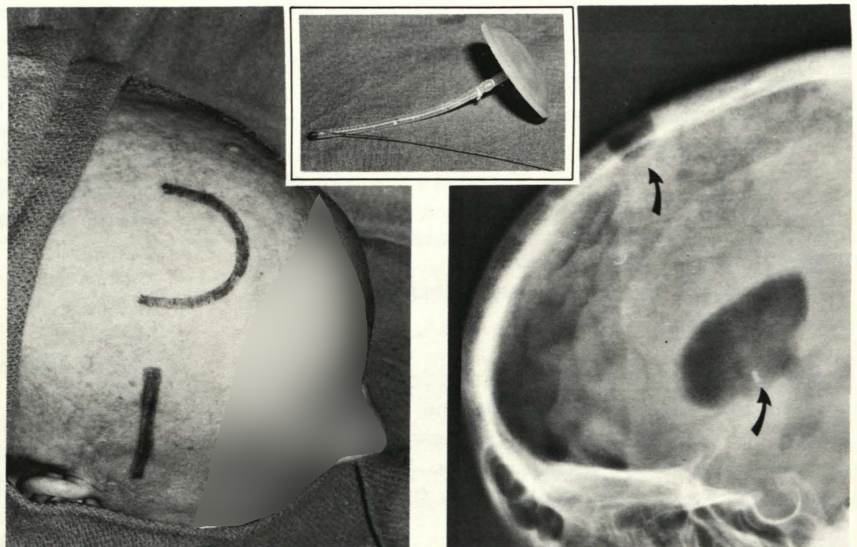
spinal chord. These sites are believed to be areas concerned with processing nociceptive stimuli. To cross the blood-brain barrier, and to compensate for biotransformation of the drug as it circulates in the body, the dose administered orally or parenterally must be large (60 mg or more in most cases). The Ommaya reservoir eliminates these problems and the need for a large dose. "With the reservoir, the morphine goes straight to the site of the receptors," Dr. Hill explained.

For this same reason, the side effects of lethargy and sedation, resulting from large doses required with the other methods of drug administration, are ameliorated. Dr. Hill theorizes that the low dose and immediate binding to the opiate receptors prevent the drug from binding to other cells in the body. "We use such a low dose that there is not much left after the drug binds to the receptors; what is left cannot pass through the blood-brain barrier into the body very easily."

Insertion of the Ommaya reservoir is a simple operation requiring the patient to receive a local anesthetic. The reservoir is now only inserted in the head, a more convenient location than the spine for drug injection. Made of Silastic, the reservoir has a 3.4-cm diameter and is attached to a Silastic catheter 7.25 cm long. To implant the reservoir, the neurosurgeon makes a U-shaped incision on the scalp in the right frontal region of the head and pulls the scalp flap back. The incision is slightly larger than the diameter of the reservoir. A circle of pericranium the size of the reservoir is excised and a burr hole drilled through the right

*Continued on page 2*

*The Ommaya reservoir (center), 3.4 cm in diameter, is attached to a catheter 7.5 cm long. When placed in the head (using the removable metal stylette), the device delivers morphine directly to the central nervous system. The inverted U-shaped incision line (left), drawn on the patient's scalp over the medial aspect of the right coronal suture, outlines the placement site of the reservoir. The line drawn on the right side of the head marks the catheter extension from the calvarium to the floor of the lateral ventricle. A postoperative right lateral x-ray of the head (right) illustrates the burr hole drilled through the right coronal suture (top arrow) and the catheter tip near the floor of the lateral ventricle (bottom arrow).*



## Ommaya Reservoir . . .

*Continued from page 1*

coronal suture. The dura is then opened to allow visualization of the frontal cortex. A needle is inserted through the burr hole to the horn of the ventricle, and air is injected into the ventricle to delineate it. After the needle is removed, the catheter, attached to the reservoir, is passed along the same path so that the catheter tip reaches the roof of the ventricle and penetrates it. The catheter is further advanced until the reservoir rests on the calvarium.

The position of the catheter tip is checked with a lateral skull x-ray. If the reservoir is properly placed, the surgeon sutures the reservoir to the pericranium on the outside of the calvarium and pulls the flap of scalp over the reservoir. Cerebrospinal fluid from the ventricle enters the reservoir. The reservoir may be used 48 hours after the operation and is generally filled every 8 to 12 hours thereafter depending on the patient. A patient's relative or friend can learn to fill the reservoir with a simple injection through the scalp flap. The patient and those administering the drug also learn aseptic techniques in caring for the injection site.

Although the Ommaya reservoir has displayed good results, there are some limits to its application. Experience has shown that the reservoir is most effective for alleviating pain associated with tissue damage by a tumor. In addition, because of the slight risks of surgery, the reservoir is recommended only for those patients who are responding poorly to morphine administered orally or parenterally, have strong family or friend support, and have an expected longevity of at least a month. The Ommaya reservoir can offer a solution to a wide range of problems facing a

## New Book Published

The 1982 *Year Book of Cancer*, 26th in a series of timely briefings representing a broad spectrum of oncologic literature, is now available (Year Book Medical Publishers, Inc., Chicago, 1982, 477 pages, \$39.95). Edited by R. Lee Clark, MD, Russell W. Cumley, PhD, and Robert C. Hickey, MD, this volume contains 271 article abstracts, representing approximately 100 journals. Chosen from the oncologic literature of the past year, the contents reflect a number of trends, including: Cancer etiology and prevention; the use of computerized axial tomography for cancer diagnosis, staging, therapy planning, and follow-up; the development of new surgical techniques; and advances in the field of immunology.

patient with this profile, providing pain relief, freedom to leave the hospital, and, in some cases, economic relief, as well.

The device can be used for extended periods, Dr Hill said, citing the example of a young woman who has used the reservoir for more than a year without complications. Although morphine injected through the reservoir may cause some nausea 30 minutes to an hour after the injection and constipation, there has been no evidence of respiratory depression. Most patients using the Ommaya reservoir have limited life expectancies; complete pain relief and reduction of side effects allow them to lead relatively normal lives.

Illustrating the benefits of the reservoir, Dr Hill related the story of a woman suffering severe pain from carcinoma of the cervix. "When it became clear that the disease was progressing and the patient was not responding to treatment, she asked to spend her last days at home in another city," he explained. But two problems stood in the way: She was receiving continuous infusions of morphine with an infusion pump, which required hospitalization, and her insurance would cover the cost of the infusion (up to \$150 a day) only if she were in a hospital or extended-care facility in the Houston area.

"She was a good candidate for the Ommaya reservoir and decided to undergo the operation. "We cut her morphine dose to a hundredth of what she had been getting," Dr Hill said. Pain relief with the infusion pump necessitated administration of 1800 mg of morphine each day; with the Ommaya reservoir, relief was accomplished with only 18 mg each day (9 mg injected every 12 hours). Use of the reservoir reduced expenses to a nominal level. Because her husband was able to give the injections, the patient was no longer dependent on the infusion pump and was able to go home.

When she died 2 months later, she was receiving 27 mg of morphine every day; as often happens, she had developed a tolerance to the drug. However, Dr Hill explained, the Ommaya reservoir freed her to enjoy her last weeks at home, alert, and without pain.

(Physicians desiring additional information should write or call C. Stratton Hill, MD, Department of Internal Medicine, MDAH Box 8, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, (713) 792-2824.—ED)

## OncoLog

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# New Drug Combination Improves Survival For Patients with Metastatic Prostate Cancer

by Christopher J. Logothetis, MD, Department of Internal Medicine, Melvin L. Samuels, MD, Department of Internal Medicine, Andrew C. von Eschenbach, MD, Department of Urology, Antonio Trindade, MD,\* Sheryl Ogden, BSN, Department of Internal Medicine, Cindy Grant, BS,\* and Douglas E. Johnson, MD, Department of Urology

This article is a summary of a paper that first appeared in *Journal of Clinical Oncology* 1 (6):368-379, June 1983.

According to American Cancer Society estimates, 23,000 men died last year in the United States of prostatic cancer, the second most common malignancy in men after lung cancer. Infrequent early diagnosis accounts for this high mortality; almost half (45%) of all patients have metastatic disease at diagnosis, and of these only 20% survive 5 years.

Because many patients have metastatic disease refractory to standard hormone therapy, various chemotherapeutic agents have been investigated. We have found the combination of doxorubicin, mitomycin-C, and 5-fluorouracil (DMF) to yield a higher objective response rate in these patients than other single- and combination-drug regimens investigated to date.

The different response criteria used in various drug studies and the clinical heterogeneity of disseminated prostate cancer have complicated the comparison of different drug regimens. For this reason, our study was planned not only to test the effectiveness of DMF chemotherapy, but also to devise a standard staging system and response criteria for patients with hormone-refractory metastatic prostate cancer.

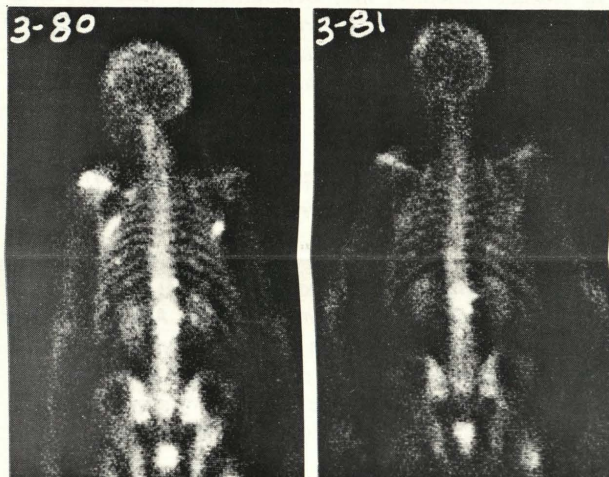
## Methods

Sixty-two patients were treated with DMF chemotherapy between December 1979 and October 1981. The median age of the study population was 63.5 years.

All patients had histologically verified adenocarcinoma of the prostate, the cell type found in 95% of all prostatic malignancies. Excluded from the study were patients with transitional cell carcinomas of the prostatic ducts. The patients were considered to be hormone refractory if, in addition to subjective deterioration after hormone therapy, they demonstrated progressive disease by bone scan, rising serum acid phosphatase or alkaline phosphatase, or the development of new metastases. Patients were not excluded from the study because of an expected poor survival or poor performance status. Exclusion criteria included the presence of overt congestive heart failure and bone marrow failure attributed to radiation therapy. Patients who had received prior chemotherapy were also excluded.

Forty-eight patients (77.4%) received radiation therapy prior to initiation of chemotherapy: 26 (41.9%) had radiation therapy to the pelvis only, whereas 22 (35.5%) had radiation to the pelvis and extrapelvic sites. All patients received hormone therapy prior

\*No longer at UT MDAH.



Bone scans of a patient with stage O<sub>1</sub> (Osseous 1) metastatic prostate cancer at initiation of DMF chemotherapy (left) and a year later (right) provide evidence of skeletal disease regression after treatment.

to chemotherapy: 49 were treated with diethylstilbestrol and orchiectomy, 11 with diethylstilbestrol alone, and 2 with chlorotrianisene.

Clinical evaluation included a complete history and physical examination, bone scan, bone survey, chest x-ray, intravenous pyelogram, electrocardiogram, cardiac scan, serum acid phosphatase, serum alkaline phosphatase, SMA-12, and complete hemogram. Computerized tomography of the abdomen and pelvis and lymphangiography were performed on selected patients.

The treatment regimen consisted of DMF delivered intravenously to outpatients. The first 22 patients received doxorubicin, 50 mg/m<sup>2</sup> of body surface area, on day 1 of each course, 5-fluorouracil, 750 mg/m<sup>2</sup> on days 1 and 2 of each course, and mitomycin-C, 10 mg/m<sup>2</sup> on day 1 of each course. By dividing the dose of doxorubicin and mitomycin-C on two subsequent days (doxorubicin, 25 mg/m<sup>2</sup> days 1 and 2; mitomycin-C, 5 mg/m<sup>2</sup> on days 1 and 2), emesis was significantly ameliorated. This modification was adopted for the last 40 patients studied.

The three-drug combination was delivered at increasing intervals between courses; the duration of each interval was determined by marrow recovery. In the absence of marrow recovery due to tumor infiltration, a granulocyte count of more than 2,000/mm<sup>3</sup> and a platelet count of more than 100,000/mm<sup>3</sup> was required prior to administration of a subsequent course of chemotherapy. Although we had initially planned not to decrease the drug dose, 3 patients required a 20% dose reduction because of persistent thrombocytopenia. The 12 patients with central nervous system involvement received 2,500 rad to the single most threatened central nervous system site simultaneously with

Continued on page 6

## Leukocyte Interferon Inhibits Growth

by *Helmuth Goepfert, MD, Department of Head and Neck Surgery, Jordan U. Gutterman, MD, Department of Clinical Immunology and Biologic Therapy, William J. Dichtel, MD,\* Roy B. Sessions, MD,† Ayten Cangir, MD, Department of Pediatrics, and Marcelle Sulek, MD†*

*This article is a summary of a paper that first appeared in Annals of Otolaryngology, Rhinology & Laryngology 91:431-436, July-August 1982.*

Juvenile laryngeal papillomatosis is the most common benign proliferative condition in the larynx of children. Also found in less aggressive forms in adolescents and adults, laryngeal papillomas have a relentless propensity for recurrence and a befuddling lack of behavioral predictability. For this reason, standard surgical treatment is often only temporarily successful, and repeated surgery is usually required.

Alternative treatments, such as cryosurgery, diathermy, ultrasonography, radiotherapy, steroid hormones, cytotoxic drugs, biologic response modifiers, and CO<sub>2</sub> laser vaporization (the most popular recent method) have been investigated. The general philosophy of management using these methods has been to control the growth of the papillomas with minimum danger to normal tissues in the hope that the aggressiveness of the tumor will diminish in time. In line with this philosophy, UT MDAH in collaboration with Baylor College of Medicine conducted a study of interferon (IFN) for this disease. The results indicated that IFN may be one of the most effective and least toxic treatments for this virally related tumor.

It is assumed that juvenile laryngeal papillomatosis is induced by a papilloma virus, a subgroup of the papova viridae family. Papilloma viruses are both host- and tissue-specific; they induce epithelial and fibroepithelial tumors in skin and mucosal epithelia and are thought to be responsible for cutaneous lesions as well as mucosal papillomas, such as laryngeal and anal-genital warts.

Interferon was chosen as treatment for juvenile laryngeal papillomatosis because of its antiviral, antiproliferative, and immunomodulating effects, clearly demonstrated with myxovirus and herpes simplex virus. By itself, IFN has no direct antiviral action; however, it does induce synthesis of intracellular enzymes that act to control viral growth. Patients in this study were treated with human leukocyte (alpha) IFN, a type of IFN induced by viruses and used in most clinical trials.

### Methods

Fourteen patients with aggressive laryngeal or laryngotracheobronchial papillomatosis were included in the study (Table 1). Ten patients were male, and 4 were female. There were 4 adults, 2 adolescents, and 8 children (less than 10 years old); ages ranged

from 2 to 35 years. All patients were white. Three patients had papillomas in all three possible areas: Larynx, trachea, and bronchi. The adult patients had required two or more therapeutic endoscopies within the preceding year, and all children had four or more such procedures during that time. All patients had undergone numerous endoscopies previously; 2 patients had had more than 60 procedures, and 1 patient had over 300 endoscopies in his lifetime. Eight patients had previously required or were currently dependent on tracheostomy. Six patients had had major crises during their illnesses, such as acute airway obstruction or cardiopulmonary arrest.

Before the patients were admitted to the study, detailed histories were taken, and physical examinations were performed. Complete blood counts, platelet counts, liver function studies, serum urea nitrogen levels, creatinine determinations, and chest roentgenograms were obtained. Direct laryngoscopy and appropriate laser vaporization were performed on all patients prior to initiation of IFN treatment. Patients underwent monthly laryngoscopies during the first 3 months of treatment and at 2- to 3-month intervals thereafter, as dictated by clinical progress. Eleven of the 14 patients underwent laryngoscopies by the same surgeon. The extent and distribution of papillomas were recorded diagrammatically in each case.

During each patient's treatment, complete blood differential and platelet counts were obtained weekly for the first month of treatment, twice a month during the second, and monthly during the remainder of the period of IFN administration. Liver and renal function studies were performed monthly for the first 3 months of treatment and subsequently on a bimonthly basis.

Alpha IFN was obtained from the Finnish Red Cross and Blood Transfusion Laboratories, Helsinki, Finland. The initial daily dose of IFN was 2 million units/m<sup>2</sup> of body surface area administered intramuscularly. The frequency of administration was changed to three times weekly whenever the papilloma growth rate decreased or remained stable over two successive endoscopies. Furthermore, dose reduction (to 1 million units/m<sup>2</sup>) or changes in frequency of dose administration were called for whenever the white blood cell (WBC) count dropped below 2500/cu mm or the level of serum glutamic oxaloacetic transaminase (SGOT) rose above 100 units/ml. If toxicity persisted despite dosage changes, IFN was temporarily discontinued until blood test values returned to normal. Withdrawal of the patients from IFN therapy was considered on an individual basis.

Response to treatment was determined by evaluation of the diagrammatic representation of disease recorded at the time of each endoscopy. Categories of response were: Complete response, no evidence of papillomas present in the laryngotracheobronchial area; good response, an estimated 75% reduction of the overall papilloma volume; moderate response, 50 to 75% estimated reduction; and slight response, 25 to 50% reduction. Any reduction in papilloma size was assumed to represent a response to IFN. If no discernible reduction in growth occurred or if growth increased, it was considered a negative response.

\*No longer at UT MDAH.

†Formerly of the Department of Otolaryngology, Baylor College of Medicine, Houston, Texas.

# Of Virally Related Laryngeal Tumor

TABLE 1. Summary of Characteristics of Patient Population\*

Patient	Sex	Age (yr)	Onset Age (yr)	Papilloma Natural History			IFN Treatment			
				Location	Crisis <sup>†</sup>	Endos	Months	Toxicity	Initial Response	Sustained Response
1	M	3	1.5	Larynx	Yes	Many	7	Slight-liver	Slight	Yes
2	M	35	32	Larynx	No	Many	11	Slight-liver, WBC	Complete	Yes
3	M	3	1.5	Larynx/trachea (tracheostomy)	No	Many	11	Slight-liver, WBC	Complete	Yes
4	M	9	6	Larynx	No	Many	6	Marked-liver, WBC	None	—
5	M	30	25	Larynx (tracheostomy)	Yes	Many	10	None	Complete	No-grew at 7 mo
6	F	5	3	Larynx	No	Many	7	Marked-liver	Complete	LTF at 8 mo
7	F	2	1	Larynx, TBP (tracheostomy)	Yes	Many	12 <sup>‡</sup>	None	Moderate	No-grew at 6 mo
8	M	26	2	Larynx (tracheostomy)	No	60+	11	None	Complete	No-grew at 4 mo
9	M	27	2	Larynx (tracheostomy)	No	300+	9	None	Good	Yes
10	M	12	5	Larynx	Yes	60+	12	Moderate-liver, WBC	Good	No
11	F	8	5	Larynx (tracheostomy)	Yes	Many	11	Moderate-liver, WBC	Good	No-grew at 4 mo
12	M	14	4	Larynx, TBP (tracheostomy)	No	Many	7	Slight-WBC	Slight	Yes
13	M	4	2	Larynx, TBP (tracheostomy)	Yes	Many	12	None	Moderate	Yes
14	F	8	—	Larynx	No	Many	4	Marked-liver	Slight	No

\*Abbreviations are as follows: IFN=Interferon; WBC=White blood cell; TBP=Tracheobronchial pulmonary involvement; LTF=Lost to follow-up.  
<sup>†</sup>History of either respiratory obstruction necessitating tracheostomy or cardiorespiratory arrest.  
<sup>‡</sup>Continuing.

## Results

Twelve of the 14 patients completed a minimum of 7 months of IFN therapy. Patient 4 was removed from the study because of continued toxicity (primarily SGOT elevation) despite dose modifications. Patient 14 was removed from the study at parental request after the first signs of significant liver toxicity. These patients had shown no response or slight response while receiving the drug.

The responses were distributed as follows among the 12 evaluable patients: 5, complete response (2 having sustained responses); 3, good response (1 sustained); 2, moderate response (1 sustained); and 2, slight response (2 sustained).

Of the 5 patients with complete response, there were 3 adults and 2 children (3 and 5 years old). All the adults showed complete or good response. The 2 patients in whom slight responses were seen were 3 and 14 years of age. Six of the 12 patients who responded sustained the initial response throughout the entire period of IFN administration. The remaining 6 responding patients failed to sustain the initial tumor response. There was no apparent correlation between the degree of initial response and its duration.

Nine patients were evaluated while receiving the drug for periods longer than 7 months: 3 patients for 12 months; 4 patients

for 11 months; 1 patient for 10 months; and 1 patient for 9 months. Nine patients have had follow-up examinations at least 1 month after cessation of IFN treatment. Two of these patients (1 and 12) had slight increases in growth since IFN withdrawal. Two other patients (9 and 11) had marked and moderate increases in growth, respectively. Patient 13 showed a transient diminution of disease for approximately 1 month after cessation of treatment followed by renewed growth of papillomas. Patients 2, 3, 5, and 6 have been followed for 1 to 3 months without any signs of increased growth. Patients 2 and 3 remain free of disease.

Toxicity was evaluated in all 14 patients initially entered in the study. Of the 9 patients who demonstrated signs of toxicity, 3 showed complete responses, 2 had good responses, 3 had slight responses, and 1 had no response. Neither of the 2 patients with moderate responses demonstrated any toxicity.

Temperature elevation was common during the first few injections of IFN but did not appear after the patients had received multiple doses. Malaise, fatigue, and slight anorexia were not ignored but were usually thought to be of minor significance. As a matter of fact, the infants who showed marked regression of tumor usually became more active and had increased appetites. Opportunistic infections did not occur.

White blood cell drop (below 2500/cu mm) and elevation in the

*Continued on page 8*

## Prostate Cancer . . .

Continued from page 3

the first course of chemotherapy.

To compare response to treatment of subgroups of patients, we adopted a unique clinical and prognostic staging system. The staging system employed four clinical categories: Osseous I ( $O_I$ ), axial skeletal involvement; Osseous II ( $O_{II}$ ), axial skeletal plus diaphyseal and distal extremity involvement; Visceral I ( $V_I$ ), parenchymal lung metastasis; Visceral II ( $V_{II}$ ), visceral involvement, other than lung (usually liver, brain, or mediastinum). Patients who otherwise would be classified in the  $O_I$  or  $V_I$  category but had bone marrow failure attributed to tumor infiltration of the marrow cavity or renal failure (serum creatinine  $> 2$  mg/dl) were placed in their respective stage II categories ( $O_{II}$ ,  $V_{II}$ ). Nodal metastases were thought to be present in all patients prior to involvement of the skeleton or viscera and, therefore, were not considered in the staging system unless the mediastinum was involved. Patients who had osseous metastases and mediastinal disease were placed in the  $V_{II}$  category. Although we encountered no patients with nodal metastases as the only manifestation of recurrent hormone-refractory prostate cancer, such patients would be included in the  $O_I$  category.

The response criteria employed throughout the study required an improvement in all parameters used. To be considered responders, the patients had to have a 50% reduction in their elevated serum alkaline phosphatase level or acid phosphatase level on three separate occasions. Patients with abnormal bone scans were required to show an improvement in bone scan results. If visceral metastases were present, greater than 50% reduction in the sum of the perpendicular diameters of each lesion was required; if lytic metastases were present, blastic healing was required. No clinical deterioration attributable to tumor growth or new metastatic sites could develop. Responses were initially assessed after completion of the second course of chemotherapy. Patients who received radiation therapy simultaneously with the first course of chemotherapy had to show improvement in sites other than the irradiated site to be considered responders. A complete response required the total resolution of all initially abnormal laboratory, radiographic, and bone scan findings. The duration of response was calculated for patients in each of the clinical categories of disease and for the total population.

### Results

Of the 62 patients, 30 (48%) met the criteria for an objective response to chemotherapy. Responses were obtained in 12 of 23 patients (52%) with  $O_I$  disease, 6 of 18 (33%) with  $O_{II}$  disease, 8 of 9 (88%) with  $V_I$  disease, and 4 of 12 (33%) with  $V_{II}$  disease. Patients with  $V_I$  disease had a significantly better response rate ( $P < 0.02$ ) than those with  $O_{II}$  or  $V_{II}$  disease.

Kaplan-Meier survival plots were generated comparing responders and nonresponders in the total population. Survival times were calculated from the day of initiation of chemotherapy. A significant survival benefit was demonstrated for responding patients (Wilcoxon signed-rank test,  $P = 0.001$ ). The median

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37th Annual Symposium  
On Fundamental Cancer Research

## Mediators in Cell Growth and Differentiation

March 6-9, 1984

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Cochairpersons: Richard J. Ford, Jr, MD, PhD, Department of Pathology, and Abby L. Maizel, MD, PhD, Department of Pathology

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survival of the responding patients was 47.5 weeks, while the nonresponding patients survived a median of 23.8 weeks.

No patient achieved a complete remission. Of the 8 responding patients with  $V_I$  disease, 2 had complete resolution of pulmonary metastases, but because bone scans failed to normalize, they were not considered to have had complete remission. Among the 30 responding patients, bone scan improvement was marked in 17, while the remaining responders had distinct but less striking objective improvement.

The duration of response was highest among patients with osseous metastases. The median duration of response was 11 months for patients with  $O_I$  disease, 9.5 months for those with  $O_{II}$  disease, 6.5 months for patients having  $V_I$  disease, and 5 months for those with  $V_{II}$  disease. The mean response duration for the total population was 8.73 months with a range of 3 to 19 months and a median of 7.5 months. Many of the responding patients continued to respond; therefore, the response duration would be expected to increase with a longer follow-up.

Kaplan-Meier survival plots were made comparing the survival of all patients in each of the four clinical stages. The median survival was 54.5 weeks for patients with  $O_I$  disease, 26 weeks for those with  $O_{II}$  disease, 33.8 weeks for patients with  $V_I$  disease, and 26 weeks for those with  $V_{II}$  disease. Patients with  $O_I$  disease survived significantly longer than the other patients (Wilcoxon signed-rank test,  $P = 0.001$ ). No differences were found in the mean or median ages of patients in each of the clinical categories. The presence of central nervous system involvement in 12 patients did not adversely influence survival.



The majority of patients suffered nausea and vomiting from at least one course of chemotherapy. Despite this, the regimen was well tolerated by outpatients. Stomatitis was unusual. Alopecia was universal. Common complaints were asthenia and anorexia. Myelosuppression occurred in 15 patients (24%). Of these, 6 patients required platelet transfusions, and each of these patients had bone marrow failure due to tumor or radiation therapy. Despite the advanced age of this population and frequently associated cardiovascular disease, only 1 patient developed doxorubicin cardiomyopathy. No patient suffered the reported hemolytic uremic syndrome attributed to mitomycin-C. One patient was suspected of having suffered the idiosyncratic interstitial pneumonia due to mitomycin-C. Three patients suffered fatal complications: One from a pseudomonas sepsis, a second from an interstitial pneumonia clinically thought to be induced by a virus or mitomycin-C, and a third from disseminated varicella.

#### Discussion

The high objective response rate among patients treated with DMF who met accepted criteria for tumor measurement contrasts to the paucity of objective responses reported with other regimens. Among patients treated in the National Prostate Cancer Project trials, the overwhelming majority of responding patients were those achieving stabilization. The combination of 5-fluorouracil, doxorubicin, and cyclophosphamide was investigated in another study in 21 patients; 5 (29%) achieved a subjective response, and 1 showed improvement in bone scan; no mention of response in patients with visceral metastases was made. The combination of doxorubicin and cyclophosphamide, in another study, failed to achieve an objective response in 3 patients with abnormal chest x-rays. In an additional study, none of 4 patients with lytic metastases treated with the combination of melphalan, methotrexate, prednisone, vincristine, and 5-fluorouracil demonstrated blastic healing; however, 4 of 5 patients presenting with lytic metastases in our study achieved blastic healing with DMF chemotherapy.

An integral part of treatment in our study was the use of radiation therapy in conjunction with DMF chemotherapy for patients with neurologically threatening lesions. Neurologic complications are frequent in prostate cancer. Most neurologic complications are caused by local extension of osseous metastases resulting in central nervous system compromise. Osseous metastases often respond sluggishly to chemotherapy; therefore, the simultaneous use of radiation therapy with the first course of chemotherapy is essential to the aggressive management of neurologically threatened patients.

We believe DMF chemotherapy is effective in the treatment of hormone-refractory prostate cancer. The regimen, causing moderate toxicity, achieved a 48% objective response rate and palliated pain. These results were obtained with a study population at high risk for toxicity due to heavy prior radiation therapy and advanced disease at presentation.

The staging system and response criteria used identified subpopulations of patients and allowed for simple and accurate comparison of data related to these subpopulations: Patients with only axial skeletal metastases, O<sub>I</sub>, survived significantly longer than those in the remaining three clinical stages ( $P = 0.001$ ); patients with osseous metastases, O<sub>I</sub> and O<sub>II</sub>, achieved more

durable responses than patients with visceral metastases, V<sub>I</sub> and V<sub>II</sub>; patients with O<sub>I</sub> disease often had an indolent course even in the absence of a chemotherapy response; and patients with O<sub>II</sub>, V<sub>I</sub>, V<sub>II</sub> disease who failed to respond to chemotherapy rapidly succumbed to their disease. No significant survival differences were seen among patients with O<sub>II</sub>, V<sub>I</sub>, and V<sub>II</sub> disease, even though patients with V<sub>I</sub> disease had a higher response rate and those with O<sub>II</sub> disease a more durable response.

These differences among subpopulations should have important clinical implications if confirmed in a larger population. Such confirmation will require the development of new chemotherapy strategies tailored to the needs of each clinical category of metastatic prostate cancer.

(Physicians desiring additional information should write or call Christopher J. Logothetis, MD, Department of Internal Medicine, MDAH Box 77, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, (713) 792-2830.—ED)

The University of Texas  
M. D. Anderson Hospital and Tumor Institute  
at Houston

## *The Administrative Aspects of Cancer Chemotherapy*

February 3, 1984

Four Seasons Hotel  
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Houston, Texas

Cochairperson: Donald B. Wagner, MHA  
Associate Vice President for Patient Care Operations

This conference is designed for hospital administrators and directors of nursing and pharmacy to answer administrative questions regarding cancer chemotherapy. Areas to be discussed include legal and medical risks associated with mutagenic exposure, disposal recommendations for chemotherapeutic agents, and the handling of chemotherapeutic agents.

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## Leukocyte Interferon . . .

*Continued from page 5*

SGOT level (above 40 units/ml) indicated a toxic reaction. Two of the 9 patients with toxicity were taken off the study because of persistent side effects. In the remaining 7 patients, depression of the WBC or elevation of the liver enzyme was totally reversed by alteration of IFN dose or cessation of the drug altogether.

No correlation between response and the susceptibility of the patient to IFN toxicity was seen. It is noticeable, though, that of the 8 patients who were under 10 years of age, 6 demonstrated SGOT elevations, and 3 of these 6 patients had myelosuppression as well. Only 1 of the 4 adult patients showed mild liver enzyme elevation and a slight bone marrow suppression. From these numbers, it appears that age of the patients is an important factor in tolerance to IFN.

### Discussion

Not only are there variations in the natural history of juvenile laryngeal papillomatosis from patient to patient, but in time different patterns of aggressiveness may be seen in the same patient. Several internal and external influences on the host, some of which escape our present knowledge, induce variations in the behavior of this benign tumor and add to the difficulty of treating the disease. More aggressive forms of the disease in the larynx, which is the site of most frequent involvement, or over the mucosa of the trachea and bronchi have necessitated the use of a variety of treatments other than surgical ablation. Interferon, with its antiviral and immunomodulating effects, was hoped to be especially effective in treating this proliferative, virally related tumor.

By study design, it was required that all of our patients have aggressive papillomatosis; this may have had some influence on response to IFN treatment. Most patients in our study continued to receive IFN for more than 9 months without a substantial increase in the response rate. By and large, the beneficial effects of the drug were noticed within 6 to 12 weeks of initiation of therapy.

For accurate determination of response, careful documentation of disease within the larynx and the tracheobronchial tree is mandatory. Photographic records of the laryngoscopic findings will only reflect the superficial and more proximal appearance of

the papillomas and certainly will fall short of any tumor volume determination. Graphic-pictorial documentation used in this study depends on the accuracy of the observer. We believe that our having one endoscopist perform follow-up studies on the majority of the patients and graphically document results provided the most accurate, objective evaluation.

In our study we used the IFN preparation originally developed by Cantell of the Finnish Red Cross Blood Transfusion Center and the Central Public Health Laboratory in Helsinki. The preparation's purity is approximately 1%. Lymphoblastoid IFN and IFN obtained through the recombinant DNA technology are of 80–95% purity, respectively. Furthermore, it has been shown that the alpha IFN obtained by the Cantell method is probably a mixture of several subtypes of IFN, each one with a specific activity.

Our data suggest that the relatively impure preparations of alpha IFN used here can lead to the regression of papillomas. We are hopeful that further studies of more pure forms of IFN for patients with laryngeal papillomas of a variety of clinical presentations will yield even better results.

(Physicians desiring additional information should write or call Helmuth Goepfert, MD, Department of Head and Neck Surgery, MDAH Box 69, The University of Texas M. D. Anderson Hospital and Tumor Institute at Houston, 6723 Bertner Avenue, Houston, Texas 77030, (713) 792-6920.—ED)

## Question/Answer

**Q:** *What is the value of the occult blood test in cancer detection?*

**A:** The stool guaiac slide test (occult blood test) is an easy, painless, and inexpensive test to detect the presence of occult blood in the stool, a common sign of colorectal cancer.

In patients with early disease, occult blood in the stool often may be the only sign or symptom present. This fact may account for the less than 50% detection rate for early localized colorectal cancers. Because prognosis is related to the extent of disease at diagnosis, as many as 75% of patients with colorectal cancer might be cured if the disease were detected early enough. The occult blood test is of great significance in detecting early disease and potentially reducing mortality associated with colorectal cancer.—Anthony J. Mastromarino, PhD, Vice President for Research