Metronidazole and Interstitial Implantation in the Treatment of Extensive Recurrent Head and Neck Cancers

LEO E. ORR, MD,* AJMEL PUTHAWALA, MD,* A. M. NISAR SYED, MD, FRCS (EDIN AND LOND), DMRT,*† AND PETER A. FLEMING, MD*

Twenty-three patients with recurrent or persistent epidermoid carcinoma of the oral cavity, all of whom had failed primary antitumor therapy, were treated with interstitial irradiation and a radiosensitizer. Such primary therapy had included radical surgery, external radiation therapy, or a combination of both. All patients underwent afterloading interstitial iridium-192 implants. Each subject received 6 g/m^2 metronidazole administered orally in one dose every 48 hours for the duration of the implant. The radiation dose ranged between 4500 and 6500 rads in 65 to 120 hours. Sixteen of 23 patients (69.6%) demonstrated complete regression of local disease, usually within 12 weeks. Ten of the 23 individuals (43%) remain alive and disease-free with an average follow-up of 25 months since the completion of the regimen. Neurologic and hepatic toxicity were notably absent. Nausea, mild diarrhea and accentuation of the radiation-induced mucositis constituted the principal side effects. *Cancer* **48:43–47, 1981.**

THE SUCCESSFUL CONTROL of solid tumors with ionizing irradiation has been limited for several reasons. Hematogenous spread often exists at the initiation of radiotherapy. The tolerance of normal tissue to irradiation, when adjacent to the tumor, rarely exceeds 4000–6000 rads over a four- to six-week period of time. Efforts to overcome this problem have been attempted with the use of iodine-125 and iridium-192 implants.[20] However, the major reason for radiation failure is related to new growth of tumor at the primary site from more resistant cancer cells which have survived the erstwhile lethal action of radiation treatment. This is felt to represent the most important factor in the poor local control achieved with the irradiation of certain tumors, principally some central nervous system malignancies and head and neck carcinomas.[11,12] Large variations in the radiosensitivity of cells present in any given malignancy will occur because of differences in the concentration of available oxygen present at the time of radiation therapy. A fraction of these cells will remain characteristically anaerobic because, by nature, a tumor will outgrow the supply of oxygen carried to it by the vascular system. There is sufficient evidence now to indicate that such hypoxic cells are the radioresistant ones which limit radiocurability.[1,5,14]

Several methods of overcoming this problem have been used clinically, including the administration of hyperbaric oxygen during radiation therapy, radiotherapy with heavy nuclear particles such as neutrons from cyclotrons, hyperthermia, optimum size and spacing of multiple doses of conventional radiation therapy, and, most recently, the use of chemical radiosensitizers. Radiosensitizers mimic the sensitizing effects of oxygen in terms of irradiation and are active only against hypoxic cells. They increase the therapeutic ratio in that they do not increase the radiation response in well-oxygenated normal tissues.[4] Most agents that have been utilized have limitations based on erratic absorption and metabolism and frequency of side-effects. The drug metronidazole has been more widely used because of the absence of the above problems. This drug appears to effectively sensitize hypoxic malignant tissue to radiation therapy; it is not rapidly metabolized, so that infrequent doses can be used; it can penetrate malignant tissues far from vascular capillaries: and it has a high therapeutic ratio and little systemic toxicity.[2,7,9,19] Indeed, the agent has proved

Presented at the American Society of Therapeutic Radiologists ASTR Conference, New Orleans, Louisiana, October, 1979.

From the *Department of Medical Oncology and Radiation Medicine, California Hospital Medical Center/Southern California Cancer Center, Los Angeles, California, and the †Department of Radiation Medicine, University of Southern California/Los Angeles County Medical Center, Los Angeles, California.

Address reprint requests to Leo E. Orr, MD, Department of Medical Oncology and Radiation Medicine, Southern California Cancer Center, 1414 South Hope Street, Los Angeles, CA 90015.

Accepted for publication January 21, 1981.

0008-543X/81/0701/43/$0.80

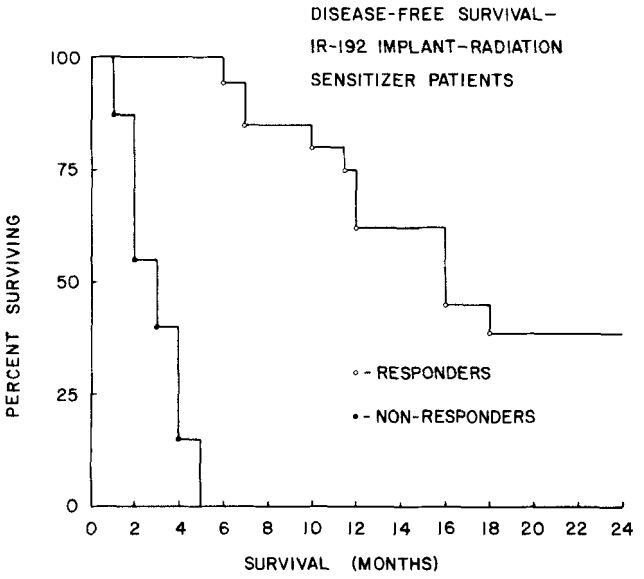

FIG. 1. Comparative disease-free survival in patients responding to the radiosensitizer–radiation regimen.

to be useful in treating anaerobic bacteria and parasites such as Bacteroides and entamoeba.

Most investigators evaluating the concomitant use of radiation therapy and radiosensitizers in human solid tumors include trials of patients with glioblastoma multiforme.[22–25] Indeed, in studies of patients with blastoma who received metronidazole and concomitant external irradiation therapy, remission was significantly prolonged over a similar group receiving radiation therapy alone.[22,24]

Head and neck carcinoma, particularly epidermoid carcinoma of the head and neck, would appear to be an ideal malignancy in which to exploit the radiosensitizer concept. This is a common primary solid tumor with limited radiation sensitivity, having a large number of hypoxic cells, and many cells in the early phases of the cell cycle, mainly the G_0–G_1 phases.[15] These features would be even more applicable to patients who had received previous external irradiation therapy and had failed. A pilot study was thus launched to examine the metronidazole–radiation therapy concept when applied to the treatment of previously irradiated and inoperable head and neck carcinoma.

Methods

The pharmacokinetics of metronidazole have been well studied in normal tissues, in malignant astrocytoma and squamous cell lung cancer, principally from work performed by Urtasun and others.[7,23] It was planned that a sufficiently high dose of this drug be used to assure reasonable blood levels of metronidazole during the duration of the interstitial implantation. Pertinent pharmacokinetics are summarized elsewhere.[24]

Metronidazole blood levels were determined by spectrophotometric and gas chromatographic methods. The spectrophotometric method described by Urtasun[26] is based on the light absorbance characteristics of alcohol solutions of metronidazole at 314 nm.

Serum proteins were precipitated with alcohol and the O.D. of the supernatant was determined at 314 nm with a Beckman DV spectrophotometer. Since serum contains many chemicals that absorb light at 314 nm, a premedication serum sample is needed for a blank. In the absence of a premedication serum sample, an average O.D. of many normal sera is substituted for a blank. The use of a calculated blank results in decreased accuracy and specificity of the test results.

In order to perform serum levels of metronidazole with greater accuracy and specificity, a gas chromatographic procedure was established in the laboratory by Dr. James Larsen. A standard curve for both procedures is calculated with standard solutions of pure metronidazole (supplied by Searle Laboratories, Chicago, IL).

In the present study, all patients placed on protocol had epidermoid carcinoma of the head and neck previously given "curative treatment" with surgery and irradiation and they had had maximal doses of external irradiation therapy. The majority of these individuals had primary malignancies of the tongue, soft palate, pharynx, tonsils, and floor of the mouth, 60% having undergone radical surgery, and 18% experiencing and failing subsequent chemotherapy.

The study group was selected from a total implant schedule which included 106 patients seen over a 36-month period of time. The selection was made because of the large local recurrences present in this group, many of whom had necrotic tumor centers. It was felt that these 23 patients had the worst prognoses of the entire patient schedule and that any benefits to be had from the combination therapy might be appreciated more distinctly.

All patients received orally 6 g/m^2 metronidazole six hours prior to the implant and then every 48 hours for up to three doses. Serum metronidazole levels were obtained on each patient every other day. Patients who demonstrated hepatic, renal, hematologic or peripheral neurologic dysfunction before being placed on the protocol were excluded from the study. The extent of the response was measured in terms of data gathered from measurements of residual tumor, from surveys for distant metastases, and in terms of survival after the definitive procedure. Each patient's performance status as adjudged by the Karnofsky scale, weight gain, improvement in nutritional status, appearance of metas-

tases, days in the hospital following the procedure and frequency of pain medication, were specific factors also useful in assessing the overall nature of the response. Patients were treated with iridium-192 after-loading implants in a manner described elsewhere.[20]

Results

All patients have been followed from a minimum of 18 months to 35 months. The tumor dose of the iridium-192 brachytherapy administered ranged from 4500 to 6000 rads over 65 to 120 hours. In most patients some regression of the implanted malignancy appeared several days after the procedure, however, regression was maximal by the fourth week after implantation. There was considerable local mucositis at the time that the implant was removed, often lasting up to two weeks. Only local emollients were required for tissue healing. Among 23 patients studied, 16 (69.5%) were responders with complete regression of all discernible tumor. Improvement in nutritional status, pain quality and performance status followed in most such individuals. Four patients had partial responses. Ten patients (43%) have had no evidence of recurrent disease following the procedure. The actual disease-free survival for this group extends from nine to 35 months with a mean disease-free survival period of 24 months. The status of this group has not changed at the time of writing. Nonresponders had an average survival of nine weeks. This information is summarized in Figure 1 and Table 1.

Complications of the implant included local tissue necrosis in one patient; two cases of osteoradionecrosis of the mandible; and more frequent acute mucositis referred to earlier (Table 2). Acute mucositis appeared to be much more common in the responders. The complications of this schedule of metronidazole administration were few and included self-limiting nausea, diarrhea, cephalgia and one episode of dark urine. No hematologic, hepatic or neurologic toxicity was noted. Those who responded appeared to be slightly better nourished in terms of level of serum albumin and the extent of pretreatment weight loss. However, there were no other outstanding differences between the two groups studied (Table 3). Six of the 23 metronidazole–implant subjects were able to gain weight after the procedure. Only one responder developed overt metastases during the period of observation. Metastases were apparent in three of those who did not respond and appeared within 11 weeks of the interstitial implant. The metronidazole plasma levels did not appear to have predictive value in terms of response. Most of the individuals appeared to absorb the drug in a uniform manner, although the half-life was slightly different throughout the group.

TABLE 1. Metronidazole–Iridium-192 Treatment of Head and Neck Malignancy–Two-year Status of Responders

Total patients	23
Complete responders	16
Partial responders	4
Patients alive	16
N.E.D. at 20 months	10
Disease-free survival for responders*	9–30+ months
Mean disease-free survival	24 months
Survival of nonresponders	7–18 weeks (mean 9)

* Actual survival.
N.E.D. = no evidence of disease.

TABLE 2. Complications of Radiosensitizer—Iridium-192 Treatment

Metronidazole	No. patients	Implant	No. patients
CNS toxicity	0		
Nausea	2	Local tissue necrosis	1
Diarrhea	1	Osteoradionecrosis of mandible	2
Headache	3		
Dark urine	1	Acute mucositis	10
Myelodepression	0		
Hepatotoxicity	0		
Peripheral neuropathy	0		

Discussion

An effort to exploit the concept of radiosensitizers in head and neck carcinoma has been attempted for the last 15 years (see Table 4). The agents used have principally included actinomycin because of the well-known augmentation of radiation effect seen in almost every organ when this drug is used. More recent efforts have included the use of adjunctive bleomycin, doxorubicin and mitomycin-c for similar reasons.[19] The improvement in local tumor control has been modest at best. The therapeutic ratio is not enhanced with these combinations since normal tissues also have an enhanced susceptibility to radiation damage when these antibiotic-derived antitumor agents are used. In any case, these drugs have an additive value in

TABLE 3. Characteristics of Radiation Sensitizer—Implant Study Group

	Responders	Failures
Age (years)	59	54
Nodal metastases	1	2
Postimplant infection	2	0
Serum albumin	3.6	2.7
Hemoglobin	14.7	13.2
Lymphocyte count	2662	1980
Neutrophil count	3164	3281
Pretreatment weight loss of 10% body weight	3	3

TABLE 4. Compounds that Significantly Modify Radiation Effects

Radiation-enhancing agents	Radioprotective agents
Nitroimidazoles	Cysteamine
Metronidazole	Aminoethylisothiouronium
2-Nitroimidazole (ro-07-0582)	
Halogenated pyrimidine analogs	
5-Bromodeoxyiodine	
5-Chlorodeoxyuridine	
5-Fluorodeoxyuridine	
Nitrofurans	
NDPP	
Actinomycin	
Bleomycin	
Anthracycline derivatives	
Doxorubicin	
Daunorubicin	
Mitomycin-C	

terms of effecting local control, but have been inappropriately dubbed radiosensitizers.

The halogenated pyrimidines have been employed for a number of years as radiosensitizers in animal tumors. However, human application has been limited by the presence of severe local mucosal toxicity.[13,14] The mechanism of action includes the replacement of true thymidine with the halogenated thymidine during DNA replication; except for 5-fluorodeoxyurdine which inhibits the enzyme thimidylate synthetase. The radiosensitivity of the cell is thus increased because of the presence of the halogen in the replicating DNA as it is exposed to ionizing radicals. Unfortunately, normal tissues are affected in a similar fashion.

The only useful radiosensitizers have been the nitroimidazoles. These drugs are electron-affinic compounds that mimic the effect of oxygen by increasing free-radical production in hypoxic tumor cells, thereby increasing the radiotherapeutic effect. The high degree of penetration of most body tissues, whether well-vascularized or hypoxic, may help to explain the action of these compounds. It is possible that direct cytotoxicity from the nitroimidazole alone may contribute to the intensification of the antitumor effect, sensitizing intracellular DNA to radiation-induced damage. There are a number of agents in the category, but only metronidazole and 2-nitroimidazole, or misonidazole have been investigated to any large degree. 2-Nitroimidazole is more effective on a milligram per milligram basis than is metronidazole. However, toxicity data are still conflicting for 2-nitroimidazole and it is uncertain as to whether the safety features of this drug parallel those of the 5-substituted compound.[4,8,21]

Head and neck carcinoma patients in gross relapse after "curative" surgery or radiotherapy survive on the average three to four months without therapy. Chemotherapy has not improved overall survival. The iridium implant is becoming a very useful means of secondary therapy for these people and appears to be an ingenious method of circumventing the appearance of irreversible normal tissue damage. The availability of an effective well-tolerated radiosensitizer when combined with the after-loading implant modality appears to engender a synergistic effect in terms of cell-kill. The foregoing information and the numbers of patients analyzed are insufficient to form conclusions as to the long-term effectiveness of this combination in preventing local complications and metastases, although augmented survival is suggested. The present pilot study suggested that enhanced local tumor control was achieved using the metronidazole implant technique and that survival was extended in the responding group. Whether the data is applicable to the average patient with head and neck cancer remains to be seen.

The chemical modification of the radiation response could likely be effectively applied to other human solid tumors such as sarcomas, pancreatic cancer, inoperable gastrointestinal malignancies, and bronchogenic carcinoma. Since those drugs that are selective radiosensitizers and those that have only an enhancing effect have different toxicities, it seems likely that many could be used in conjunction. One might consider the concurrent administration of small amounts of cancer chemotherapeutic agents such as bleomycin or mitomycin-c and hypoxic cell sensitizers for head and neck cancer. Adriamycin and a hypoxic cell sensitizer could be utilized for the treatment of sarcomas or pancreatic carcinoma. The evaluation of sensitizers in combination with high linear energy transfer irradiation represents another avenue of investigation.

This pilot study will be extended to include alterations in the dose schedule of a nitroimidazole in head and neck cancer patients undergoing interstitial implantation.

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