COMBINED MODALITY THERAPY WITH 5-FLUOROURACIL, MITOMYCIN C AND RADIATION THERAPY FOR SQUAMOUS CELL CANCERS


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The eradication of epidermoid cancers of the anal canal by an empirically developed program of concurrent radiation, 5-Fluorouracil (5FU), and Mitomycin C (MTC), was described by Nigro, Vaitkevicius and Considine in 1974. The rapid and complete tumor response obtained in the first three patients encouraged these investigators, and subsequently others, to evaluate the combination in patients with squamous cell carcinomas in different sites. It is perhaps fortuitous that epidermoid anal carcinomas were treated first, for the results in that site have generally been the most striking, and even then some authors have questioned whether similar results could not have been achieved with simpler regimens.

The three agents included in this treatment protocol have been studied as single agent treatment for many years. Radiation therapy is long established as a treatment for squamous cell carcinomas and frequently produces both local control and cure. 5-Fluorouracil, a fluoropyrimidine, produces responses in from 10 to 20 percent of patients with advanced squamous cell carcinomas in various sites. Mitomycin C, which acts principally as an alkylating agent, has been used in fewer studies than 5FU, but is also reported to produce responses in from 10 to 20 percent. There is much less information about the response of squamous cell carcinomas to combinations of 5FU and MTC. Michaelson et al (1983) recently reported a 59% response rate in patients with advanced epidermoid anal cancer. A trial conducted by the Southwest Oncology Group showed partial responses in 4 of 10 patients with disseminated esophageal cancer (Rosenberg et al, 1982). Most of these responses to either single agent or combined chemotherapy were partial and lasted only a few months.

The general principles and objectives of combining chemotherapeutic agents and radiation therapy have been reviewed extensively (Fu, 1985; Peckham et al, 1981). Although most investigators studying combinations of 5FU, MTC and radiation (FUMIR) have retained the concurrent administration of the agents as described in the original protocol, it is worth noting that, in general, the concurrent administration of drugs and radiation frequently enhances normal tissue effects, while tumor effects have a more variable dependence on the timing of chemotherapy and radiation (Fu, 1985). The justification for the concurrent use of 5FU and radiation in this protocol is based on both clinical and laboratory evidence. In the case of MTC, however, concurrent administration may not be necessary.
Prior to the introduction of FUMIR in Detroit (Nigro et al, 1974) there had been few studies of concurrent 5FU and radiation in squamous cell cancer. Gollin et al (1972) had reported improved local control and survival, but increased acute toxicity, in patients with advanced head and neck cancer treated by intravenous bolus injections of 5FU concurrently with radiation. Because the Detroit group had demonstrated that a continuous infusion of 5FU produced less myelosuppression than daily bolus injections (Seifert et al, 1975), they elected to study this schedule of 5FU administration in their FUMIR protocol. As Byfield discusses elsewhere in this volume, this may have been a fortunate choice, for in his laboratory studies with adenocarcinoma cell lines, any sensitizing interaction between radiation and 5FU was strongly dependent on concurrent use of the agents, and the interaction was also dependent on the maintenance of cytotoxic levels of 5FU over a continuing period, in a way more analogous to continuous infusion than to bolus injection. Studies with MTC have demonstrated that at low concentrations, similar to those which can be achieved in humans by bolus injections, any effects of MTC and radiation on aerobic cells appear to be additive (Rockwell, 1982). The data on any possible interaction on anaerobic cells is more limited, but it has been demonstrated that, under experimental conditions, MTC is more toxic to cells that are hypoxic at the time of drug treatment than to well oxygenated cells (Teicher et al, 1981). It has been speculated that this differential cytotoxicity might be an advantage when MTC is combined with radiation in the treatment of tumors containing hypoxic cells, since such cells are relatively radioresistant. The minimum concentration of MTC necessary for true radiosensitization was calculated to be 4 ug/ml (Rockwell, 1982), about four times the peak plasma levels attained in humans by bolus injections of 10 to 30 mg (Reich, 1979). It is, of course, quite possible that none of these laboratory experiments is relevant to the clinical treatment of squamous cell carcinomas by fractionated courses of radiation combined with chemotherapy, but it is clear that further studies of this kind will be needed to enable more directed development of the empirical schedules currently employed in the clinic.

While the theoretical bases for the use of FUMIR are not yet resolved, many clinical studies have been reported. At the Princess Margaret Hospital (PMH), we have evaluated the response to FUMIR of squamous cell cancers in several sites. The main areas of interest have been anal and esophageal cancer, head and neck cancer, and uterine cervical cancer. The results achieved in these tumor sites at PMH, and elsewhere, are presented here.

PRINCESS MARGARET HOSPITAL TREATMENT SCHEDULES

The schedules used most frequently at PMH for the treatment of carcinomas of the anal canal, esophagus, and head and neck are summarized graphically in Figure 1. Schedule A involves external beam megavoltage radiation alone to a tumor dose of 5000 cGy in 20 fractions in 4 weeks. This radiation dose is retained in Schedule B, but in Schedule C the radiation course is split into two segments, each of 2500 cGy in 10 fractions in 2 weeks separated by a 4 week interval. In Schedule B, a single bolus intravenous injection of Mitomycin C, 10 mg/m², is given on day 1, and a 4 day continuous intravenous infusion of 5-Fluorouracil, 1000 mg/m²/24 hours, is given on days 1 through 4. In the split course Schedule C, the same chemotherapy is given over the first 4 days of each of the radiation courses. For all primary tumor sites, the maximum dose of 5FU is restricted to 1500 mg/24 hours, and for esophageal and head and neck carcinomas the maximum dose of MTC is restricted to 15 mg. These dose restrictions were decided upon arbitrarily and other investigators have used different doses.