5-Fluorouracil, Adriamycin, and Mitomycin in the Treatment of Adenocarcinoma of Unknown Primary

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The combination of 5-fluorouracil (5-FU), doxorubicin, and mitomycin (FAM) is often recommended for empiric management of patients with adenocarcinoma of unknown primary. This recommendation is based on the activity of FAM for adenocarcinomas of specific known sites of origin. A literature search disclosed no reports of the efficacy of FAM in this clinical entity. We report on 45 patients with biopsy-proven adenocarcinoma in whom investigation revealed no primary site and who were treated in a phase II trial with FAM. Of 43 evaluable patients, four achieved a complete tumor response, and nine obtained a partial response for an overall response rate of 30%. The median survival for all patients was > 10 months. The median survival for patients whose tumors were unresponsive to FAM was 6 months, and median survival was ≥ 14 months in patients with stable disease or FAM-responsive tumors. A phase III trial comparing no therapy or 5-FU with FAM is warranted. For patients not treated in an investigative setting, FAM compares favorably with reported series using other regimens.
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THE PATIENT with an unknown primary carcinoma represents one of the most difficult and common problems faced in clinical oncology. It has been estimated that such cases constitute as many as 10% to 15% of the solid tumor patients referred to a medical oncology service.[1] In general, the profession has taken a rather conservative approach to the management of this presentation for several reasons. Despite an extensive and costly diagnostic evaluation, the probability of identifying the primary tumor ante mortem is only 9% to 17%,[2,3] although the introduction of routine abdominal computed tomography (CT) scanning has provided a 32% correct diagnosis in a recent small series.[4] The survival of patients with metastatic adenocarcinoma of unknown primary is characteristically measured as a few months.[1,5–7] In carefully selected patients, typically those who are ambulatory but symptomatic, the use of empirically derived forms of chemotherapy has been deemed justified, but there is presently no accepted standard drug treatment. Moertel et al have reported an overall 12% objective response rate in 160 patients who were treated primarily with intensive courses of 5-fluorouracil (5-FU); however, the median survival of this group was only 4 months.[1] More recently, Woods et al have compared the efficacy of two forms of combination chemotherapy, doxorubicin (Adriamycin; Adria Laboratories, Columbus, Ohio) and mitomycin (Mutamycin; Bristol Laboratories, Syracuse, NY) (DM) *v* cyclophosphamide (Cytoxan; Mead Johnson Pharmaceutical Division, Evansville, Ind), methotrexate, and 5-FU (CMF).[8] Nine of 25 patients (36%) treated with DM were reported to have responded, compared with one of 22 receiving CMF. The overall median survival of the study population was only 13 weeks, and 18 weeks with DM treatment.

Increasingly, the regimen of 5-FU, doxorubicin, and mitomycin C (FAM) has been recommended and used in the management of the patient with an unknown primary carcinoma, but without a published data base to support this practice.[9–11] The FAM program was originally developed for the treatment of advanced gastric cancer in which a 42% response rate was reported.[12] Subsequently, efficacy was demonstrated for adenocarcinomas of the pancreas and lung.[13,14] This served as a rationale for the selection of FAM as an empiric treatment since the latter two neoplasms represent the most common entities in patients in whom an unknown primary is eventually diagnosed ante or postmortem.[2] This report provides the first description of the

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efficacy of the FAM combination for the treatment of patients with adenocarcinoma of unknown primary.

METHODS

The patient population consisted of 45 patients with histologically proven adenocarcinoma for whom a primary tumor could not be defined. There were 23 men and 22 women with a median age of 61 years (range, 32 to 79). The median performance status, as assessed using the Eastern Cooperative Oncology Group (ECOG) system was 1 (range, 0 to 2). Two patients had received chemotherapy before referral. Two patients were not evaluable. The sites of measurable disease included lung, liver, lymph nodes, or subcutaneous, abdominal, or mediastinal masses. In addition to a thorough physical examination, the minimum diagnostic evaluation included routine hematologic studies and serum chemistries, including liver function tests as well as a chest x-ray. Additional tests were performed as described in Table 1; these were individualized in each case based on the histologic features of the tumor as well as symptoms or evidence of organ dysfunction that served to direct the work-up to possible sites of primary cancer.

Table 1. Diagnostic Tests in the Work-up of 43 of 45 Patients With Adenocarcinoma of Unknown Primary

Test	No. of Patients Undergoing Tests
Thyroid scan	12
Chest x-ray	43
Chest tomograms	11
CT scan–chest	7
CT scan—abdomen	23
Barium enema	34
Upper GI series	36
Laparotomy	10
Intravenous pyelogram	22
Sonogram (abdominal and/or pelvic)	24
Mammogram	16
Liver-spleen scan	26
Bone scan	22
Bronchoscopy	12
Transurethral resection of prostate	2
Arteriogram	2
Cystoscopy	4
Brain scan (CT or radionuclide)	5
Gastroscopy	8
Colonoscopy	6
ERCP	2
Lung scan	1

Abbreviations: GI, gastrointestinal; ERCP, endoscopic retrograde cholangiopancreatography.

NOTE: The median number of tests per patient was eight.

The tests do not include serologic tumor markers such as carcinoembryonic antigen (CEA) or α-fetoprotein. In two patients, access to medical records of testing at other institutions was denied.

The experimental nature of the regimen was explained and consent obtained in the usual manner. The FAM regimen was administered in 8-week cycles. Treatment was continued until disease progression with deletion of doxorubicin at a cumulative dose of 400 mg/m^2. 5-FU was administered at 600 mg/m^2 on days 1, 8, 29, and 36; doxorubicin was administered at a dose of 30 mg/m^2 on days 1 and 29; and mitomycin C was administered at a dose of 10 mg/m^2 on day 1 only of each course. Drug dosage was modified in subsequent courses based on the degree of hematologic toxicity as measured by WBC and platelet counts as previously reported.[12] Blood counts were obtained weekly during the first course of chemotherapy and in subsequent cycles before each treatment. Because the nadir of hematologic toxicity produced by mitomycin C occurs 4 to 5 weeks after administration, blood counts measured during this period were used to adjust the dosage of this agent for the subsequent cycle.

A complete response (CR) required the disappearance of all evident tumor for at least 2 months. A partial response (PR) was defined as a 50% or greater decrease in the products of the two largest perpendicular diameters of the most-clear lesion; this must have occurred without an increase in the size of other known areas of malignant disease or the appearance of new metastases, and must have lasted at least 2 months from the initiation of therapy. In the interest of minimizing discomfort, radiation exposure, and cost, not all lesions were evaluated at all cycles in patients with intraabdominal disease who had a more accessible measurable metastasis. If hepatomegaly was the measurable lesion, a decrease of at least 50% in the sum of measurements below the xiphoid process and costal margins at the midclavicular line was required. Radionuclide liver scans were used to measure response if the lesion seen on the scan was > 5 cm in diameter. Stable disease was defined as no increase in any measurable tumor, no development of new sites of tumor, and no obvious clinical deterioration. Duration of response and survival were measured from the start of therapy.[15]

RESULTS

Of 43 evaluable patients, four achieved a CR, and nine obtained a PR for an overall response rate of 30%. The median duration of CR was 17 months (range, 10 to 26 months). The median duration of PR was 10 months (range, 4 to 31 months). Five patients evidenced stabilization of tumor growth for a median of 12 months (range, 2 to 84 months).

Four patients survive at this writing: one stable patient, one PR, one CR, and one with progressive disease. The median survival of all patients in the series is > 10 months, with 44% alive at 1 year. The 20 patients who achieved CR, PR, or disease stability evidenced a median survival of > 14 months, whereas the median survival of the complete responders was > 18 months (range, 11 to 72+ months). The sample size of responding patients is small and precludes any significant comparison regarding survival among patients with CR *v* PR. For those patients who

failed to achieve a response, the median survival was 6 months (Fig 1). There was no association between site(s) of tumor and chemotherapy responsiveness.

The FAM regimen was moderately well tolerated. Leukopenia of ECOG grade 2 or greater was observed in 12 patients. One patient had grade 3 (WBC, 1,700/μL) and two patients grade 4 toxicity (WBC, 900/μL in both). There were two episodes of neutropenia-associated bacterial septicemia, one of which resulted in the patient's death despite hospitalization and intravenous (IV) antibiotics.

Thrombocytopenia of ECOG grade 2 or greater occurred in nine patients. Five patients had grade 3 thrombocytopenia (platelets, 25 to 50,000/μL). One patient had an exsanguinating gastrointestinal (GI) hemorrhage from a documented necrotic tumor. The platelet count during this episode was 22,000/μL.

Three individuals had ECOG grade 2–3 mucositis without sequelae. One patient with a history of severe chronic obstructive pulmonary disease died of refractory right-sided congestive heart failure after receiving a cumulative dose of 100 mg/m^2 of doxorubicin. Permission for autopsy was denied. Despite the low cumulative dose and lack of pathologic correlation, doxorubicin must be implicated in the exacerbation of cardiomyopathy. The hemolytic uremic syndrome, characterized by hemolysis, thrombocytopenia, and renal failure, first manifested 14 months after FAM administration was begun, proved fatal in one responding patient.[16] Although permission for autopsy is requested in all deaths occurring in the hospital, permission was denied in all cases.

DISCUSSION

Because of the recognized poor prognosis of the patient with adenocarcinoma of an unknown primary, a focused attempt to identify the site of origin is recommended so that specific forms of therapy can be applied. Moertel and others reported in 1972 that the organs involved at presentation provided a better projection of survival than the identity of the primary site.[1] Since that report, advances in imaging, principally the CT scanner, provide noninvasive means to help pinpoint the primary site of occult malignancy. Histochemical advances can identify lymphoma, germ cell tumors, prostate cancer, and breast cancer so that informed therapeutic choices can be made.[17–20] Advances in therapy can result in striking responses in advanced adenocarcinomas including breast, gastric, ovarian, and thyroid cancers and in undifferentiated tumors including small-cell lung cancer, lymphoma, and germ cell neoplasms. Two factors have been emphasized in our general diagnostic strategy: the relative incidence of certain cancers and their innate responsiveness to treatment.

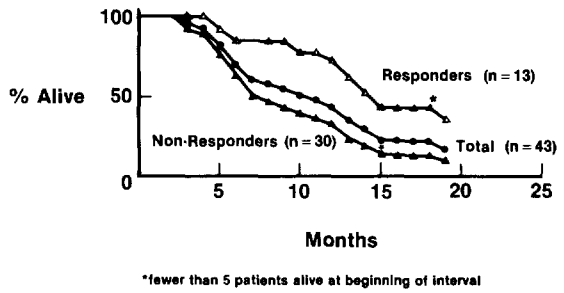

Fig 1. Time from diagnosis to death.

However, despite a careful physical examination, review of the histology by an informed pathologist, and the appropriate use of specialized diagnostic procedures, the primary tumor will not be found ante mortem in the majority of patients in whom the original site of cancer is not demonstrated during the initial evaluation. It is for this group of patients that consideration must be given to the empiric use of cytotoxic chemotherapy to complement the application of local radiotherapy for palliation of symptoms. Left untreated, the median survival of this patient group has ranged from 2 to 10 months in reported series.

Historically, the treatment of unknown primaries has involved the use of 5-FU either singly or in combination with alkylating agents such as carmustine (BCNU) (Table 2). A retrospective analysis of this approach conducted at the Mayo Clinic demonstrated a 12% response rate and a median survival of 4 months.[1] Comparisons with other reported series are made difficult by the heterogeneity of tumor types and differing biology of the constellation of neoplasms that compose this generic designation. As an example, a trial comparing 5-FU with the regimen of 5-FU, doxorubicin, and cyclophosphamide (FAC) demonstrated no responding patients with either form of therapy,[21] whereas Valentine et al reported a 14% response rate with the FAC regimen.[22]

Table 2. Chemotherapy in the Treatment of Adenocarcinomas of Unknown Primaries

Regimen	No. of Patients	Objective Response (%)	Survival (mo)		Reference No.
			All	Responders	
F	88	16	3		1
F	65	6.2			20
F	20	0			17
T	17	23			18
M	9	22			1
CMFVN	130	6.2	6		5
Singly or in combination				24	
AM	25	36	18	28	17
FB	11	18			1
CAF	14	14		15	18
CAF	16	0			17
CMF	22	5	7		8
CAP	9	22			19
FAM	43	30	10	12	

Abbreviations: A, doxorubicin (Adriamycin); B, BCNU; C, cyclophosphamide (Cytoxan); F, 5-FU; M, mitomycin (Mutamycin); N, nitrogen mustard (Mustargen; Merck, Sharp, and Dohme, West Point, Pa); P, cisplatin; T, tegafur (ftorafur); V, vincristine (Oncovin; Lilly, Indianapolis).

Bedekian et al compared the combination of cyclophosphamide, doxorubicin, and cisplatin with single agent ftorafur (NSC 148958) and reported response rates of 29% and 24%, respectively.[23] Woods et al described a 4% response with CMF compared with 36% using doxorubicin and mitomycin C.[8]

The FAM regimen is an established therapy for gastric carcinoma and has demonstrated activity for other selected adenocarcinomas. The regimen was designed to be used as an outpatient treatment with relatively low dosage of the three drugs and an intermittent schedule. In general, patients can be treated with mild-to-moderate toxicity, and responses, when observed, occur during the first cycle of treatment. As a consequence, extended periods of toxic therapy are not required to determine whether the program will be of value in a specific case.

The results of this phase II trial in patients with an unknown primary demonstrate a modest response rate of 30%, but four patients demonstrated a CR, and there were seven patients with metastatic carcinoma with survival in excess of 2 years. The 10 months' overall median survival and 44%, 12-month survival compares favorably with all reported series using other regimens. We would recommend that FAM be considered for phase III trials comparing the three-drug combination to no therapy or to single-agent 5-FU administration. New approaches to diagnosis and therapy in adenocarcinoma of unknown primary are urgently needed.

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