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Phase II trial of dacarbazine, mitomycin, doxorubicin, and cisplatin with sargramostim in uterine leiomyosarcoma: A Gynecologic Oncology Group study

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Abstract

Objective. Following a reported 23% response rate (RR) for mitomycin (M), doxorubicin (A), and cisplatin (P) and preliminary data suggesting a superior RR for dacarbazine (D) + MAP + sargramostim, the Gynecologic Oncology Group (GOG) conducted a phase II trial of DMAP + sargramostim in patients with advanced uterine leiomyosarcoma.

Methods. Eligibility required measurable disease, a GOG performance score of 0–2, and recovery from surgery/radiotherapy. Treatment consisted of sargramostim 250 μg/m^2 SC q 12 h days −6 through −3, followed by D 750 mg/m^2 IV over 2 h, M 6 mg/m^2 IV, A 40 mg/m^2 IV and P 60 mg/m^2 IV over 2 h on day 1, followed by sargramostim 250 μg/m^2 SC days 2–15. Cycles were repeated q 28 days (if ANC $\geq$ 1500/μl and platelets $\geq$ 100,000/μl) until disease progression or toxicity prevented further therapy. Doses were to be reduced by 20% for grade 4 neutropenia >7 days or any grade 4 thrombocytopenia and by 10% for a 1- to 2-week treatment delay for myelosuppression.

Results. One of 19 patients who entered the study was ineligible. Eighteen patients received a median of 3.5 cycles (range: 1–6 cycles) of therapy. The overall RR was 27.8% (5.6% complete and 22.2% partial responses). Percent of patients with grade 3 or 4 toxicities included 78% neutropenia, 94% thrombocytopenia, 61% anemia, 44% GI, 28% infection, and 17% azotemia.

Conclusions. DMAP + sargramostim produced a 27.8% RR, but its complexity and toxicity precluded further investigation, and the study was closed after the first stage of accrual.

Keywords: Dacarbazine; Mitomycin; Doxorubicin; Cisplatin; Uterine leiomyosarcoma

Introduction

The treatment of advanced uterine leiomyosarcoma with chemotherapy has been disappointing. The Gynecologic Oncology Group (GOG) has studied a number of single agents with disappointing clinical results including objective response rates of 25% for doxorubicin [1], 3% for cisplatin [2], and 17% for ifosfamide [3]. Mitomycin C is a bioreductive-alkylating agent that has been demonstrated to potentiate the effects of cisplatin by up to 60-fold in hypoxic conditions [4,5].

Combination chemotherapy has resulted in small increments of antitumor activity with moderate additional toxicity. The combination of dacarbazine + doxorubicin has been reported by the GOG to induce tumor response in 6 of 20 patients (30%) [1]. Another study of dacarbazine + doxorubicin by the Southwest Oncology Group (SWOG) reported a 22% objective response rate in 23 uterine leiomyosarcomas [6]. The GOG previously reported a 23% objective response rate and a 6.3-month median overall survival in 35 evaluable patients with advanced uterine leiomyosarcoma [7] for the combination of mitomycin,

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doxorubicin, and cisplatin. Hematologic toxicity was substantial, with all but four patients experiencing leukopenia (median 1400/μl) and thrombocytopenia (median 62,500/μl).

Sargramostim is a commercially available granulocyte-macrophage colony-stimulating factor (GM-CSF) that induces multi-lineage bone marrow progenitor cell stimulation. Vadhan-Raj and Broxmeyer [8] demonstrated that GM-CSF rapidly increased the number of cycling myeloid progenitors and when discontinued resulted in decreased proliferation of these cells within 24–48 h. This arrested proliferation lasted up to 1 week after stopping GM-CSF. This phenomenon is not seen with filgrastim (G-CSF) [9], which stimulates only neutrophilic progenitor cells and does not result in proliferative arrest when discontinued. Therefore, GM-CSF priming can be utilized first to expand the bone marrow stem cell pool, then (by discontinuing it) to induce bone marrow stem cell arrest within 24–48 h in order to administer cytotoxic chemotherapy, and finally (by resuming it) to protect the marrow from the cytotoxic effects of the chemotherapy. Edmonson et al. previously reported a dose-escalation trial of carboplatin plus a fixed dose of cyclophosphamide 1000 mg/m^2 [10]. Four days (days −6 to −3) of marrow priming with sargramostim followed by chemotherapy on day 0 and post-chemotherapy sargramostim for 10–14 days resulted in maximal amelioration of post-chemotherapy leukopenia and thrombocytopenia. Edmonson and colleagues further reported a regimen of sargramostim 250 mcg/m^2 given subcutaneously (SC) at 12-h intervals (days −6 to −3) followed by dacarbazine 750 mg/m^2, mitomycin 6 mg/m^2, doxorubicin 40 mg/m^2, plus cisplatin 60 mg/m^2 on day 0 [11] in which patients then received sargramostim 250 mcg/m^2 SC at 12-h intervals on days 1–14 in order to accelerate bone marrow recovery. The regimen was repeated at 4-week intervals. Objective responses were seen in 11 of 18 patients with leiomyosarcoma (61%) including 8 of 10 patients with uterine leiomyosarcoma. Median survival for the latter patients was 17.5 months. This formed the basis for GOG Protocol #87K, which is the subject of this report.

Materials and methods

Eligibility

Patients with measurable (using RECIST criteria), histologically confirmed, advanced, persistent, or recurrent uterine leiomyosarcoma and no prior chemotherapy were eligible for entry into this phase II treatment trial. Eligibility also included a GOG performance status 2 or better and full recovery from previous surgery or radiation therapy. Patients were required to have adequate bone marrow function (ANC $\geq$ 1500/μl; platelets $\geq$ 100,000/μl), adequate renal function (serum creatinine < 1.5 mg/ml), and adequate liver function (AST, alkaline phosphatase, bilirubin < 2 times upper limit of laboratory normal). Participating institutions' Institutional Review Boards approved this study prior to entering patients, and all patients provided written informed consent consistent with federal, state, and local regulations prior to receiving protocol therapy.

Treatment regimen

Eligible patients were treated with sargramostim 250 μg/m^2 SC at 12-h intervals for 4 days (days −6 through −3) followed by a 2-day rest (days −2 and −1). They then received chemotherapy on day 0 consisting of dacarbazine 750 mg/m^2 IV over 2 h, mitomycin 6 mg/m^2 IV over 2–5 min, doxorubicin 40 mg/m^2 IV over 2–5 min, and cisplatin 60 mg/m^2 IV over 2 h. Sargramostim 250 μg/m^2 was administered SC at 12-h intervals on days 1 through 14. Patients were monitored with weekly complete blood counts and were evaluated for response and retreated at 4-week intervals. To be considered evaluable for response, a patient was to have an initial tumor measurement and at least one tumor measurement 4 weeks following the initiation of chemotherapy. All patients were required to have adequate bone marrow function (ANC $\geq$ 1500/μl and platelets $\geq$ 100,000/μl) prior to subsequent retreatment. If treatment was delayed by 1–2 weeks due to myelosuppression, all subsequent dose levels were to be reduced by 10%. A delay of greater than 2 weeks required discontinuation of protocol treatment. Grade 4 (Common Toxicity Criteria, version 1.0) nadir myelosuppression required a 20% dose reduction of all cytotoxic drugs for subsequent cycles. A 1 week delay of therapy due to low blood counts on the scheduled retreatment day required a 10% dose reduction of all cytotoxic drugs. Mitomycin and cisplatin were to be discontinued for serum creatinine > grade 2. Cardiac toxicity > grade 2 required discontinuation of doxorubicin on subsequent cycles. Mitomycin was discontinued for any mitomycin-related pulmonary infiltrates. Diphenhydramine and corticosteroids were permitted for allergic reactions to sargramostim. Patients were to be treated every 28 days until tumor progression or adverse effects prohibited further protocol therapy. Total cumulative doxorubicin could not exceed 450 mg/m^2.

Response criteria

This study utilized the RECIST criteria, which requires at least two consecutive tumor measurements 4 weeks apart. Complete response was defined as the complete disappearance of all target and non-target lesions and normalization of CA-125, if elevated at baseline. Partial response was at least a 30% decrease in the sum of the longest dimensions of all target lesions from baseline by physical examination or radiologic evaluation. Increasing disease was a 20% increase in the sum of the longest dimensions of the target lesion/s. Biochemical methods were not used to define response.