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Chemotherapy, Irradiation, and Surgery for Function-Preserving Curative Therapy of Primary Extremity Soft Tissue Sarcomas: Initial Treatment with I-MAP and Inhalation GM-CSF During Preoperative Irradiation and Postoperatively

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Abstract

Purpose—To determine if aerosol GM-CSF decreases the 2 year pulmonary metastasis rate for soft tissue sarcoma.

Patients and Methods—Patients with high grade soft tissue sarcomas were treated with 2 cycles of ifosfamide, mitomycin, doxorubicin, cisplatin plus granulocyte macrophage-colony-stimulating factor (GM-CSF) subcutaneous followed by 45 GY irradiation with concurrent 2 cycles of mitomycin, doxorubicin, cisplatin followed by surgery +/- intraoperative radiation or brachytherapy. Aerosol GM-CSF (250 mcg twice a day) was administered for 1 week every other week $\times$ 3 during neoadjuvant therapy as well as beginning 4 weeks postoperatively every other week $\times$ 5.

Results—39 patients were enrolled between November 2001 and April 2006. The median age was 51 years (range: 19 – 65). The median lesion size was 9 cm (range: 2.3 – 26.7). 76% experienced grade 3–4 hematologic toxicity. Twenty-four of the first 35 evaluable patients (69%, 95% CI 41–84%) were free of pulmonary metastasis at 2 years. 82% (95% CI: 70 – 95%) of patients were still alive after 3 years, with a median follow-up of 5.5 years (range: 3.4 – 7.6). 58% (95% CI: 44 – 76%) of patients remained progression-free after 3 years.

Conclusions—The addition of aerosol GM-CSF to combined chemotherapy, irradiation, and surgery for soft tissue sarcomas did not achieve the study endpoint to decrease the 2 year pulmonary metastasis rate.

Introduction

Patients with large, high grade STS of the extremity/pelvic girdle are treated by limb-salvage surgery with either pre-operative or post-operative irradiation [1, 2] or the use chemotherapy, irradiation, and surgery [3–9]. Despite the improvements in local control, metastasis remains a problem with approximately 50% of patients developing metastasis with the majority of the metastasis occurring in the lung. In our previous study, up to 15% developed pulmonary metastasis within 2 years despite aggressive chemotherapy, [7]. Novel approaches are needed to decrease pulmonary metastasis (P-METS)

GM-CSF, well known as a hematopoietic agent, has been shown to stimulate antitumor effects through continued local exposure in cancer cells. Long lasting anti-tumor immunity has already been induced in mice through the use of GM-CSF. A phase I study by Anderson et al showed that aerosolized GM-CSF at a dose of 240 mcg bid for seven days given on alternate weeks and with a rest week between treatment weeks resulted in no toxicity over the course of several months [10]. Rao et al showed that there is clinical activity for pulmonary metastasis in solid tumors with aerosolized GM-CSF [11, 12]. The rationale for the implementation of GM-CSF in the treatment of soft-tissue sarcomas comes from the above evidence and the hope that the hematopoietic properties of GM-CSF will help to offset the immunosuppressive properties of most existing antineoplastic therapies available for treating soft-tissue sarcomas and improve the 2 year P-METS rate.

Patients and Methods

Patient Selection

Patients with potentially curable histologically-confirmed nonmetastatic high grade soft tissue sarcoma at an extremity or limb girdle were selected for this study. Further inclusion criteria required the patient to be a candidate for preoperative radiation before a limb sparing surgery, at least 18 years of age, have an ECOG performance status no greater than 2, and having adequate blood parameters (ie, WBC $\geq 3500 \mu\text{L}$ or ≥ 1500 granulocytes, Platelets $\geq 150,000 \mu\text{L}$, Direct-reacting bilirubin $\leq 0.3 \text{ mg/dL}$, and Creatinine ≤ 1.2 times the institutional upper limit of normal). Patients were excluded from the study if they had a significant infection, active heart disease, symptomatic pulmonary disease, had previous cancer chemotherapy or irradiation, had metastatic disease, had either embryonal rhabdomyosarcoma or extraosseous Ewing's sarcoma, or females who were either pregnant, nursing, or of childbearing potential and unwilling to employ adequate contraception. The study was approved by the Institutional Review Board and all patients reviewed and signed the informed consent.

Study Design

This is a prospective phase II study where patients received I-MAP and GM-CSF for two 28 day cycles. I-MAP consists of 2500 mg/m^2 ifosfamide on day 1 and day 2, 4 mg/m^2 of mitomycin on day 2, 40 mg/m^2 of doxorubicin on day 2, and 60 mg/m^2 of cisplatin on day 2. Subcutaneous GM-CSF was self administered by the patient beginning 6 days prior to chemotherapy and continuing for 4 days on a twice daily dosing schedule of 250 mcg/m^2 .

The same dosing schedule was followed for 14 days after chemotherapy. Irradiation began 4 weeks after the 2nd cycle of I-MAP. The total dose of irradiation to be delivered was 4500 cGy-5000 cGy in 25 treatment fractions (180 cGy per fraction, once daily for 5 days (Monday–Friday)). In some cases, the initial field received 3960 cGy, followed by a boost to a smaller field of 540 cGy for a total of 4500 cGy. Patients received MAP × 2 on days 1 and 28 with radiation and aerosolized GM-CSF. MAP consisted of 6 mg/m² mitomycin, 30 mg/m² doxorubicin, and 45 mg/m² cisplatin. The day after initiating day 1 of MAP, patients received twice a day dosing of aerosol GM-CSF at 250 mcg for days 1–7, 15–21, and 29–35 as described by Anderson et al [10].

Patients were evaluated 4 weeks after completion of pre-operative irradiation and concurrent chemotherapy for curative surgery. Patients were allowed to receive a boost dose of radiation with either perioperative brachytherapy or IOERT (intra-operative electron radiotherapy) or intraoperative high dose rate brachytherapy (IOHDR). The choice of boost technique was at the discretion of the radiation oncologist and depended on the location and geometry of the surgical bed and surrounding normal tissues. Doses were dependent on clinical and pathologic margin status. IOERT doses ranged from 750 – 2000 cGy prescribed at the 90% isodose depth. Patients with margins > 2 mm were to receive 750 – 1000 cGy, those with negative but < 2 mm 1000–1250 cGy, those with R1 resection 1250 – 1500 cGy and those with R2 resection 1500 – 2000 cGy. IOHDR doses were the same with dose specified 5 mm from the surface of the applicator. Perioperative brachytherapy doses were 1200 – 1600 cGy in 3–4 fractions delivered twice daily 3–5 days after surgery if done with high dose rate brachytherapy and 1000–2000 cGy at a dose rate of 50–65 cGy an hour for low dose rate brachytherapy. If brachytherapy boost was not performed, an external beam boost was to be performed 2–4 weeks post-operatively, including the tumor bed plus 2–4 cm margins with 1400 cGy in 7 fractions. Four weeks postoperative, patients received the same aerosolized GM-CSF at 250 mcg twice a day for 7 days followed by 7 days of rest. This was repeated × 4 for a total of 5 weeks of postoperative aerosolized GM-CSF. Patients were followed every 3 months for 1 year; every 4 months for 1 year; and every 6 months for 2 years, and then once at 1 year. Imaging studies at each visits included MRI of the treated area and CT of the Chest with routine CBC and chemistries.

Disease Assessment

All eligible patients initiating treatment and that had at least one post-baseline disease assessment were evaluable for the primary endpoint of to evaluate the 2-year pulmonary metastatic progression rate. Tumor response was assessed using the RECIST with reevaluation every 4 weeks [13]. Radiologic studies were performed at baseline and after every two cycles (ie, every 8 weeks) of therapy to assess tumor response.

Survival time was calculated as the time from registration to death due to any cause. Progression free survival was calculated as the time from registration to death or disease progression, whichever was first. Duration of I-MAP response was calculated from time of first response on I-MAP therapy to the time of progression. Patients who did not progress prior to surgery were censored at the date the surgery was performed. The disease free interval after surgery was calculated as the date of curative surgery to the date of progression

and for patients having been rendered disease-free at surgical debulking. If a patient died without progression then progression at death was assumed unless documentation to the contrary was available. All patients were followed for a maximum of 10 years from registration or death, whichever was earlier.

Statistical Methods

The primary endpoint of this trial was 2 year pulmonary metastatic free rate (2 year P-METS-free). All eligible patients who underwent protocol specified therapy were assessed for the primary and secondary endpoints. The 2 year P-METS-free rate was calculated as the number of patients free from P-METS after two years divided by the total number of evaluable patients. A Three-Outcome phase II study design (2001) with a planned interim analysis was used to assess whether the 2 year P-METS free rate was at least 90% (clinically promising) versus at most 75% (clinically inactive). A total of 35 patients were to be enrolled with a planned interim analysis in the first 13 evaluable patients. Absence of P-METS within 2 years in 11 of the first 13 eligible patients enrolled justified continuing enrollment to a total of 39 patients. The final decision rule was one of 3 outcomes: 1) “ineffective” if at most 27 patients were P-METS free at 2 years; 2) “effective” if 30 patients were P-METS free at 2 years; or 3) “inconclusive” if 28 or 29 patients were P-METS free at 2 years. This study was designed to have 90% power at the 0.05 level of significance to detect a P-METS free rate of at least 90%. Confidence intervals were calculated using the method of Duffy and Santner [14].

Summary statistics and frequency tables were used to describe baseline characteristics and adverse event information. Hematologic adverse events were collected as a minimum value (ie nadir) per course of treatment and have been converted to a common grading scale (National Cancer Institute Common Toxicity Criteria for Adverse Events, version 2.0). Attribution for all adverse events was also collected. The Kaplan-Meier [15] method was used to estimate survival, pulmonary metastases free survival, and progression free survival. All analysis was conducted using SAS version 8.0 (SAS Institute, Cary, NC). Two sided p-values are reported and $p < 0.05$ is considered statistically significant.

Results

Patient Characteristics

A total of 39 patients were enrolled between November 2001 and April 2006. One patient was excluded from analysis because the patient did not begin cycle 1 of I-MAP due to refusal of the patient’s insurance company to support treatment at a Mayo facility. The median age was 51 (range: 19 – 65). At study entry, the median lesion size was 9 cm (range: 2.3 – 26.5) and about 40% of patients presented with disease of the proximal extremity. Further patient characteristics are summarized in Table 1. Ninety-two % of patients completed I-MAP and subcutaneous GM-CSF. Eighty-nine % of patients completed MAP with GM-CSF and radiation, with a median external beam radiation dose of 5000 cGy (range: 4500 – 5400). Seventy-nine percent of patients underwent limb salvage surgery and all but one was rendered disease-free at that time. Twenty of 28 patients (71%) patients completed all the post-operative aerosolized GM-CSF.

Treatment Outcome

Twenty-four of the initial 35 evaluable patients were free of P-METS at 2 years (69%, 95% CI: 41–84%), which failed to meet the pre-specified criteria for efficacy. Overall, seventy-three percent (95% CI: 60% – 89%) of patients (28 of 38) were free of P-METS at 2 years. Eighty-two percent (95% CI: 70% – 95%) of patients were still alive after 3 years, with a median follow-up of 5.5 years (range: 3.4 – 7.6). Fifty-eight percent (95% CI: 44% – 76%) of patients remained progression-free after 3 years (See Table 2 and Figure 1) Sixty-nine percent (95% CI: 54% – 88%) of patients were disease free 3 years. The percent change in maximum tumor diameter at the end of neoadjuvant chemotherapy and at the end of chemoradiation therapy are shown in Figure 2. Most of the patients had stable disease (ie, within $\pm$ 20% change from baseline) during IMP, with 8 of 33 showing at least a 20% reduction in tumor size. During MAP+XRT, 18 of 30 patients continued to experience further reductions of by least 10%. For those 20 out of 28 patients that completed all 10 cycles of aerosol GM-CSF, the 2 year pulmonary metastasis free rate is 90% (CI 78–100).

Toxicity

All 38 patients were eligible for adverse event evaluation. The most prevalent grade 4 adverse events, regardless of attribution to therapy, were neutropenia (n=30), leukopenia (n=12), and thrombocytopenia (n=6). Severe adverse events experienced by patient and considered at least possibly related to study treatment are shown in Table 3. Hematologic toxicity was at expected levels for this treatment strategy. Table 4 displays toxicity by treatment phase.

Discussion

Patients with large, high grade STS are at risk of metastatic disease. Efforts to improve outcomes in this group of patients with the use of adjuvant chemotherapy have shown promising results, but the clinical benefits are still debated today [16–21]. Our study evaluated the novel approach of adding aerosolized GM-CSF to an aggressive chemotherapy regimen with the hope that we could decrease the 2 year P-METS rate. Although the aerosolized GM-CSF was well tolerated, the overall 2 year P-METS free rate observed for our trial was 73% (28/35). We did not reach our pre-specified statistical benchmark of at least 75% P-METS free at 2 years. Despite not reaching the pre-specified benchmark, our approach compares favorably with other studies using neoadjuvant chemotherapy. The RTOG using pre-operative MAID (mesna, doxorubicin, ifosfamide, dacarbazine) with radiation had a 3 year distant disease-free survival of 64% and Schuetze et al using combination chemotherapy prior to surgery had a 61% metastasis-free rate [22, 23]. It is noted, however, our previous study using neoadjuvant chemotherapy and radiation therapy without aerosolized GM-CSF had an estimated 2 year P-MET free rate of 85% [7]. So at this time, we can not justify the use of aerosolized GM-CSF as an adjuvant to decrease P-MET rate and newer approaches to control micrometastatic disease are needed.

Given the small study size, one reason this study failed to reach the primary endpoint could be that only 71% of the patients continued the maintenance GM-CSF through 10 cycles. The main reason for discontinuation was patient compliance.

The neoadjuvant approach to large, high grade tumors does provide clinical information about the response to chemotherapy and concurrent chemotherapy with radiation. In our study, only 1 patient (3%, see Figure 2) had RECIST progression after 2 cycles of neoadjuvant chemotherapy and 27% (9 of 33, see Figure 2) had MRI evidence of growth of the tumor < 20%. Even after concurrent chemotherapy and radiation therapy only 9% (3 of 33) of patients had a partial response per RECIST. Using tumor shrinkage to predict outcome has been difficult and some have advocated using PET[23]. But despite the low RECIST response rate and some evidence that these tumors actually enlarge in size (largely from necrosis) during neoadjuvant therapy, the overall survival at 3 years of 82% is encouraging. Our study results with large high grade sarcomas compares favorably with other studies. Long-term follow up from the RTOG 9514 recently reported the 5 year survival rate to be 71.2% [22] and from our previous study, the estimated 5 year survival was 80% [7].

Overall the neoadjuvant approach with chemotherapy and radiation therapy for large high grade sarcoma is feasible and the addition of inhalation GM-CSF failed reach our study endpoint to improve 2 year metastasis rate. Further study of novel agents on an adjuvant or neoadjuvant basis is needed.

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A. Overall Survival **B Time to Progression** **C Time to Pulmonary Metastases**

Fig 1.

A Overall Survival, B Time to Progression, and C Time to Pulmonary Metastasis

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Figure 2.

Waterfall Plot of %-Change of Disease Measurements and During Neoadjuvant Therapy (ie, IMAP) and Neoadjuvant Therapy+XRT

Footnote/Interpretation: Positive %-change represents tumor growth (eg, 3 of 33 patients had an increase of at least 20% from baseline at the end of IMAP therapy). Negative %change represents tumor reduction (eg, 9 of 33 had a >20% reduction in tumor burden at the end of 2 cycles of MAP+XRT).

Table 1

MC0072 Baseline Characteristics

	Total (N=38)
Age	
Mean (SD)	48.0 (13.83)
Median	51.0
Range	(19–65)
Gender	
Female	19 (50%)
Male	19 (50%)
Primary Tumor Site	
Limb Girdle	11 (28.9%)
Proximal Extremity	16 (42.1%)
Distal Extremity	11 (28.9%)
Performance Status	
0	24 (63.2%)
1	14 (36.8%)
Baseline Tumor Measurement	
Mean cm (SD)	9.5 (5.21)
Median cm	9.0
Range (cm)	(2.3–26.5)
Histology	
Synovial Sarcoma	8 (21%)
Sarcoma NOS	8 (21%)
Leiomyosarcoma	6 (16%)
Pleomorphic Sarcoma (MFH)	6 (16%)
Myxofibrosarcoma	4 (11%)
Fibrosarcoma	2 (5%)
Liposarcoma	2 (5%)
Extra Osseous Osteogenic Sarcoma	1 (3%)
MPNST	1 (3%)

Table 2**Patient Outcome**

	Estimate[*], 95% CI
Survival	
N	38
# Deaths	11
Median (95% CI)	Not yet estimable (NE)
6 month	97% (92–100%)
12 month	92% (84–100%)
18 month	90% (80–100%)
24 month	84% (73–97%)
36 month	82% (70–95%)
Time-to-Progression	
N	38
# Progressed	18
Median (95% CI)	64.1 (17.9 – NE)
6 month	82% (70–95%)
12 month	74% (61–89%)
18 month	63% (50–81%)
24 month	61% (47–78%)
36 month	58% (44–76%)
Time to Pulmonary Metastases	
N	38
# w/Pulmonary Mets	13
Median (95% CI)	NE
6 months	87% (77%–98%)
12 months	82% (70–95%)
18 months	74% (61–89%)
24 months	74% (61–89%)
36 months	71% (58–87%)

* Kaplan-Meier.

Table 3

Frequently Observed Adverse Events All Cycles of Treatment

	No. of Patients (N=38)	%
Grade 3/4 Toxicity*		
FISTULA-RECTAL	1	3
ANOREXIA	5	13
COUGH	1	3
DYSPNEA	1	3
INSOMNIA	1	3
MYALGIA	2	5
NAUSEA	12	32
FATIGUE	4	10
PAIN-PLEURITIC	1	3
STOMATITIS	1	3
ARTHRALGIA	1	3
DIZZINESS	1	3
DEHYDRATION	6	16
DYSPHASIA-PHARYN RT	1	3
HYPOTENSION	1	3
HYPONATREMIA	1	3
HYPOKALEMIA	2	5
NEUTROPENIA	35	92
SYNCOPE	1	3
CONSTIPATION	1	3
SGOT (AST)	1	3
PNEUMONITIS	1	3
ISCHEMIA-CEREBRAL	2	5
LEUKOPENIA	30	79
ANEMIA	13	34
MUSCLE WEAKNESS	1	3
DYSPEPSIA	1	3
THROMBOSIS	6	16
INFECTION-NO ANC	1	3
CONFUSION	3	8
NEURO-MOTOR	1	3
VASOVAGAL EPISODE	1	3
HYPERSENSITIVITY	2	5
THROMBOCYTOPENIA	24	63
VOMITING	9	24
TRANSFUSION-pRBC	1	3
PAIN-TUMOR	1	3
WOUND-INFECTIOUS	2	5

	No. of Patients (N=38)	%
WOUND-NON INFECTIOUS	2	5
TRANSFUSION-PLT BMT	1	3
DERMATOLOGY	1	3
FEBRILE NEUTROPENIA	7	18
INFECTION-ANC	5	13

* According to NCI Common Toxicity Criteria Version 2.0. Maximum severity per patient and type.

Table 4

Maximum Severity of Toxicity, by Phase of Study Treatment

Grade 3+ Toxicity (At least possibly related to treatment)								
IMAP/s.q. GM-CSF	Grade 3+ GM-CSF (N=38)		MAP/AGM-CSF/XRT (N=34)			Post-Op AGM-CSF (N=28)		
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
ANC	6 (16%)	24 (63)	ANC	5 (15)	19 (56)	Neuropathy	1 (4)	0
PLT	19 (50)	3 (8)	PLT	14 (41)	3 (9)			
WBC	11 (29)	6 (16)	WBC	15 (44)	9 (26)			
HGB	10 (26)	1 (3)	HGB	3 (9)	0			
Nausea	10 (26)	0	Fatigue	3 (9)	0			
Vomiting	8 (21)	0	Nausea	2	0			