Neoadjuvant Chemotherapy with Ifosfamide, Cisplatin, Adriamycin and Mitomycin (IMAP) for High Risk Adult Soft Tissue Sarcomas

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Abstract- To define efficacy of pre-operative chemotherapy in down staging of advanced non-round cell soft tissue sarcomas. From Sep 2002 to Dec 2005, 70 patients were treated by Ifosfamid, MESNA, cisplatin, adriamycin, mitomycin and subsequent surgery. Postoperatively, patients received radiotherapy in cases of microscopically incomplete resection or local recurrence. The median age of the patients was 34 years and the median tumor size was 14 cm. According to AJCC classification 46 patients had stage 3 and 24 had stage 4 diseases. The most common subtypes were MFH and leiomyosarcoma. The most common sites of tumors were lower extremity and trunk. Toxicity grades three or higher consisted of nausea, Leucopenia and infection. About 50% of the patients received G-CSF. Response to chemotherapy was assessable in 63 patients; 9 patients achieved complete response and 16 showed partial response. Disease progressed in 8 and did not change in 37. The best response was seen with MFH, fibrosarcoma and synovial sarcoma. After chemotherapy seventy percent of patients underwent complete surgery. Disease relapsed in 41 patients and twenty two patients died of metastasis. Median survival of patients was 30 months. IMAP plus G-CSF is safe and effective as preoperative chemotherapy in some subtypes of sarcomas, although the metastasis problem has not been eliminated

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Introduction

Soft tissue sarcomas (STS) in adult patients are a heterogeneous group of tumors with more than 40 different subtypes (1). While local treatment remains the mainstay for localized disease; systemic chemotherapy has an important contribution in the treatment of advanced STS. Especially, in patients with locally advanced disease that is too extensive for local treatment, systemic chemotherapy may contribute to cure provided that tumor shrinkage renders subsequent optimal local treatment possible (1).

Chemotherapy has established efficacy in reducing metastasis and prolonging survival in specific subtypes of childhood STS (like Ewing sarcoma or embryonal rhabdomyosarcoma) (2,3), but its value in most histological types of adult sarcoma remains controversial (4).

In the treatment of advanced STS First-line single agent doxorubicin delivered at standard doses of 75-80 mg/m^2 yielded a 16-27% response rate in various studies (2). Chemotherapy regimen of doxorubicin and ifosfamide is the most promising combination in comparison to doxorubicin alone because of the single agent activity of both drugs; increases response rate up to 34% (5).

In an effort to further develop curative therapy, 39 patients with localized high- grade STS received systemic chemotherapy including ifosfamide, MESNA, adriamycin, cisplatin, mitomycin (IMAP) and radiation therapy before surgery. Theoretically there is no cross resistance between ifosfamide and doxorubicin and there is additive effect of cisplatin and mitomycin.Although 5 year survival rate of 80% was reported but only 20% of the patients received the prescribed chemotherapy concomitant with preoperative irradiation and 12 patients (30%) experienced some type of disease progression (9 distant and 3 local failure).

Recently, result of a metaanalysis in the treatment of STS has shown that patients who received preoperative

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radiotherapy experienced more distant metastasis than those treated with post operative radiation (6). This different outcome may be related to the delay in surgery in the pre operative group.

Based on the mentioned data from previous studies we chose to evaluate the efficacy of IMAP without concomitant radiation therapy in the treatment of advanced, high grade STS.

Patients and Methods

This prospective phase II study was designed and carried out in the Medical Oncology Department of the Cancer Institute, Tehran, Iran. Patients ranging in age from 12 to 75 years, with diagnoses of high grade, large (>5cm) STS were enrolled in this study. Pathology was reviewed by an expert pathologist at entry. Using the American Joint Commission on Cancer (AJCC) staging system (7), patients were considered eligible if they had stage III or IV disease, were at the beginning of treatment or had received inadequate surgery for tumors in the previous six weeks. Patients with diagnoses of Ewing sarcoma family, embryonal rhabdomyosarcoma, gastrointestinal stromal tumors (GIST) or low grade tumors were not eligible for the trial.

Other eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, no functionally relevant cardiovascular disease, no prior history of malignant disease or chemotherapy, no central nervous system metastases, adequate bone marrow function (baseline absolute WBC>4×10^9 per liter, platelet count> 120×10^9 per liter) and adequate renal (serum creatinine <1.4 mg /dl) and hepatic (bilirubin< 1 mg /dl) function.

The protocol was approved by the ethics committee of the Cancer Research Center of the Cancer Institute and all patients signed written informed consent. There was no industry funding for this protocol.

Pretreatment and follow-up investigation

The following features were assessed: history, physical examination, clinical and radiological measurement of the tumor, complete blood count (CBC), serum creatinine, alkaline phosphatase, AST, ALT, LDH, chest X-ray, CT-scan of lungs, CT or magnetic resonance imaging (MRI) of the primary tumor and surroundings. Before each chemotherapy cycle, physical examination, clinical tumor measurements, CBC, liver function tests and serum creatinine were repeated. During follow-up, physical examination, blood count, liver function tests and chest X-ray were performed every 3 months.

Within seven days of registration each patient began chemotherapy, as delineated in table 1. Cycle two of this regimen followed four weeks later. After two cycles of chemotherapy, the response to the treatment was measured according to the World Health Organization (WHO) criteria, by physical examination and CT-scan or MRI (8).

After a three-week rest period, patients with responsive tumors and no distant metastases were scheduled to have curative surgical resection. After complete excision of the tumor, in cases with positive margin, external beam radiation therapy was administered. Patients with responsive tumors received four more cycles of chemotherapy after surgery. If disease progression was noted after either chemotherapy cycle, the patient would proceed to the surgery, if possible, and/or radiotherapy.

Toxicity assessment and dose modification

Toxicity was graded according to the NCI common toxicity criteria, version 2 (9). Treatment was interrupted in case of events grade 2 or higher (with the exception of alopecia, nausea, vomiting or anemia) and was not resumed until the adverse effect resolved or improved to grade 1 or 0.

Drug dosage was reduced by 25% for patients who experienced a second occurrence of a given grade 2 events or any grade 3 event. Furthermore, doses were reduced by 50% for patients who experienced a third occurrence of a given grade 2 events, a second grade 3 or any grade 4 event.

Table 1. Chemotherapy protocol [1]

Agent	Dose (mg/m^2)	Route	Treatment days
MESNA	2000	IV[2] over 24 hrs in 1 liter N/S[3]	1,2,3
Ifosfamide	2000	IV over 2 hrs in 500 N/S	1,2,3
Doxorubicin	40	IV push over 5 min	1
Mitomycin	6	IV push over 5 min	1
Cisplatin	60	IV over 2 hrs in 500 N/S	1

1- Repeated every 28 days 2- Intra venous 3- Normal saline

Treatment was discontinued if, despite dose reduction, a given adverse event occurred for a fourth time at grade 2, a third time at grade 3 event or a second time at grade 4. Granulocyte-colony stimulating factor (G-CSF) was used after the first cycle in the event of grade 2 neutropenia.

The primary endpoint was response rate (RR). Using this design, with 70 patients, we had a statistical power of 80%, at a significance level of 0.05 to detect a 50% response rate. Secondary endpoints of the study were progression-free survival (PFS) and overall survival (OS).

Table 2. Patients' characteristics (70 patients)

Characteristics	Frequency (%)
Age	
Median	34.5
Range	12-75
Gender	
Male	40(57)
Female	30(43)
ECOG Performance status	
0	15(21.5)
1	49(70)
2	6(8.5)
Greatest tumor diameter	
Median	14
Range	5-35
Histological types	
Malignant fibrous histiocytoma	14 (20)
Fibrosarcoma	7 (10)
Liomyosarcoma	8 (11.4)
Rhabdomyosarcoma	5 (7.1)
Neurogenis sarcoma	8 (11.4)
Hemangiosarcoma	2 (2.9)
Spindle cell sarcoma	6 (8.6)
Liposarcoma	5 (7.1)
Synovial sarcoma	9 (13)
Others	7(10)
Tumors stage	
Stage 3	46(66)
Stage 4	24(34)
Tumors site	
Lower extremity	23 (33)
Upper extremity	9 (13)
Limb girdle	13 (23)
Retroperitoneal	9 (13)
Visceral	7 (10)
Head and neck	6 (8)

Results

From September 2002 to December 2005, 70 patients were enrolled in this study. All patients received at least two cycles of IMAP, except one who died after first cycle of chemotherapy. All patients enrolled in the study were included in the analysis. As shown in Table 2, the median age of the patients was 34 years and the median tumor size was 14 cm. The most common tumor subtypes were pleomorphic sarcoma (MFH), leiomyosarcoma, and neurogenic sarcoma. The most common tumor sites were the lower extremity and trunk. According to the AJCC staging system, 46 patients had stage III tumors and 24 had stage IV. Two-thirds of the patients were treated in the neoadjuvant and the other third in the metastatic setting. Nine patients had metastases in the lung, six in the bone, four in the liver, three in the lymph node and three in others sites.

Chemotherapy feasibility and toxicity

In general, chemotherapy was well tolerated. Eighteen patients required dose reduction and 50% received G-CSF in the course of chemotherapy. One patient died within first month of chemotherapy due to toxicity. The frequency of chemotherapy-related toxicity is outlined in Table 3. Nausea/vomiting, leucopenia, alopecia, and infection were the most common grade 3 or 4 toxicities.

Outcomes

Overall, the radiological response to chemotherapy was assessable in 63 patients. Eight patients (11%) had progressive disease, 30 patients showed minimal response or had stable disease and 36% of the patients experienced major response (nine complete and 16 partial responses).

During follow-up (median duration 30 months), 22 patients (31%) died. A total of 41 patients experienced some type of relapse. Median relapse-free survival was 13 months (95% CI 9-17).

Table 3. Response to chemotherapy (63 patients)

Response	N (%)
Complete response	9 (13)
Partial remission	16 (23)
Stable disease	30 (43)
Progressive disease	8 (11)
Total	63 (100)

Table 4. Side effects of chemotherapy (percentage in the 298 cycles)

Side effect	Grade 1	Grade 2	Grade 3	Grade 4
Leucopenia	100	48	9	3
Anemia	30	16	1	0
Thrombocytopenia	10	1	0	0
Nausea/ Vomiting	100	30	16	3
Hemorrhagic cystitis	5	6	0	0
Infection	12	3	11	1
Neurotoxicity	44	4	0	0
Renal toxicity	7	1	0	0

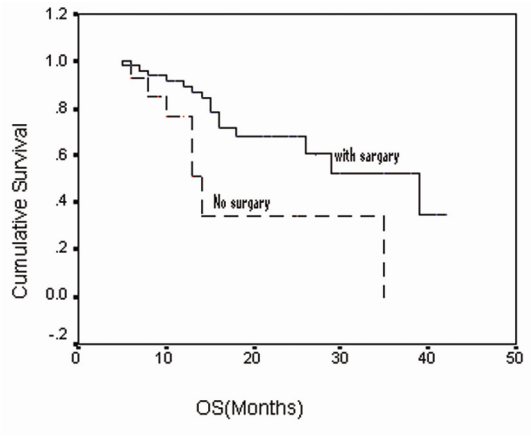

Figure 1. Overall survival based on doing surgery

Using multivariate analysis, surgery (*P*=0.006, 95% CI 1.007-1.122) and tumor size (*P*=0.03, 95% CI 1.486-10.407) were found to be prognostic factors for patient survival (Figures 1 and 2). In the preoperative group, all patients underwent surgery, including two amputations, 34 wide local excisions with negative surgical margin (R0), and 10 complete surgeries with positive microscopic margin (R1). Regarding surgical side-effects, seven patients experienced dehiscence or delay in surgery site repair, seven had infection at the site of surgery, seven experienced fever, four had cytopenia and three had deep vein thrombosis. Twenty-seven patients received red blood cell transfusion after surgery.

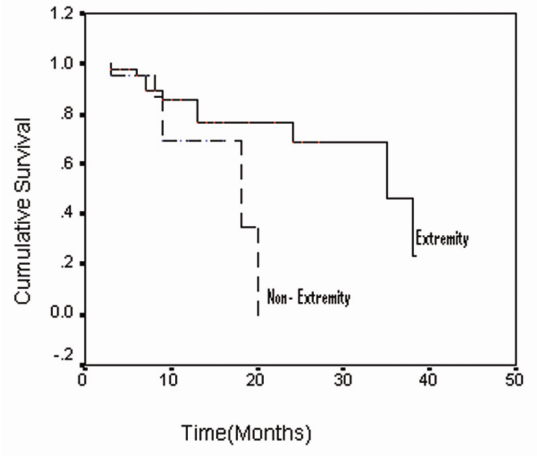

Figure 2. Overall survival based on tumor site

Discussion

This phase II study, including 70 patients with stage III or IV STS treated with the four-drug combination chemotherapy protocol of IMAP, has shown a 36% major response rate irrespective of the disease stage.

We cannot determine the relative value of this regimen versus that of other more traditional cytotoxic drug combinations, such as ifosfamide plus doxorubicin. Any critical comparison would require the development of appropriate randomized studies.

Subtypes of STS differ in terms of genetic, clinical point of view, dissemination pattern and sensitivity to antitumor agents. Despite these differences, most STS subtypes occurring in adults are similarly treated. This study included a population of high-risk patients with STS commonly considered to benefit from chemotherapy. However, the different subtypes varied greatly with regard to response rate. Certainly, angiosarcoma and neurogenic sarcomas were totally non-responsive to IMAP. Angiosarcoma of the scalp is highly responsive to paclitaxel (10), which also holds true for the combination of gemcitabine and docetaxel in patients with metastatic leiomyosarcoma (11). We strongly recommend that the diverse tumor subtypes be treated and analyzed separately for their sensitivity to systemic treatment.

Theoretically, chemotherapy is more effective in the neoadjuvant than the palliative setting. Patients who are treated in neoadjuvant setting tolerate chemotherapy much better and, if the tumor responds, can be further treated with curative surgery. In this study, the response rates to the IMAP chemotherapy were the same in both the neoadjuvant and palliative groups, although, patients in the neoadjuvant group lived longer. It is important to note that neoadjuvant chemotherapy used in this study never prevented surgery and did not necessitate a change in planned surgery. Furthermore, the chemotherapy did not exacerbate the side-effects of the subsequent surgery and/or radiotherapy. We recommend using neoadjuvant chemotherapy to enhance the resectability rate of locally advanced STS. Complete resection of the tumor was the best prognostic factor for survival in this study.

Only 18% of the patients had progressive disease with chemotherapy so, the response rate was encouraging in this trial. The median time to progression of disease was nine months and median OS was 16 months. The phenomenon of association of high tumor grade with a good but short response rate was confirmed in other studies (4). These studies strongly suggest that tumors with a higher proliferation rate are initially more sensitive to chemotherapy, although these responses are short-lived and followed by rapid progression; the consequence of which is short OS (4).

Another important point in the treatment of patients with overt metastatic disease is the balance between the toxicity of chemotherapy and the limited chance for potential benefit. In comparison to other chemotherapy protocols in the palliative setting, IMAP is too toxic in the metastatic setting (4, 12). In addition, it is especially important to use G-CSF routinely with this protocol.

There are encouraging results from preoperative concurrent chemoradiotherapy and surgical resection in the treatment of localized extremity and retroperitoneal STS. Investigators in those trials used doxorubicin as a single agent radiosensitizer in different doses and schedules. More than 80% complete microscopic resection and up to 26% complete pathologic response rate has been reported. Skin toxicity was high (30% to 40%) and rates of 26% to 35% for major wound complication after surgery were seen (13,14). Thus the issue of treatment-related wound complications should be considered in the future trials of preoperative chemoradiation for STS. One limitation of this trial was the heterogeneity of the patients, including grouping both extremity and non-extremity tumors and using the same chemotherapy protocol in both stage III and IV disease. In conclusion, IMAP chemotherapy was effective in advanced STS. This study was not able to determine whether this protocol can increase overall survival and time to progression of disease. Therefore, further prospective randomized trials and intergroup studies on special subtypes of soft tissue sarcomas are needed in order to make a more conclusive evaluation.

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