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Research Article

14 Day Continuous Infusion Ifosfamide in Advanced Refractory Sarcomas

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Abstract

Background: Ifosfamide is commonly used to treat bone and soft tissue sarcomas [STS] and its efficacy appears to increase with doses >9g/m^2/cycle. Due to the toxicity associated with bolus dosing, 14 day CIV outpatient dosing of this medication is being explored as a less toxic, convenient approach. In this study, we present the results of 47 patients who were treated with this regimen.

Methods: 47 Patients with advanced/metastic bone and STS refractory to standard therapies received 1g/m2/day x 14 days of CIV ifosfamide/MESNA; the dosing was adjusted for tolerance/toxicity. 35 patients were from a retrospective cohort and 12 patients are from a prospectively collected study. Grade 3/4 toxicities were recorded. Patients were assessed for objective response via RECIST 1.1.

Results: 47 patients received this regimen over the course of 4 years. The most common histologies were leiomyosarcoma [n=15], synovial sarcoma [n=6], HGUPS [n=6], osteosarcoma [n=4] and rhabdomyosarcoma [n=4]. 74% of patients had 2 or more lines of previous therapy. 1/47 patients had a CR [2.1%], 9/47 had a PR (19.1%) and the CBR (CR+PR+SD) was 68.1%. The median PFS was 14 weeks (range: 2-120 weeks). 60.0% patients had at least one episode of grade 3 or 4 neutropenia, 23.4% had at least one episode of grade 3 or 4 anemia and 8.5% had at least one episode of grade 3 or 4 thrombocytopenia. Of grade 3/4 non-hematologic toxicities, 5 patients [10.6%] had neurotoxicity, 1 had nausea/vomiting, 1 had congestive heart failure and 1 patient died while receiving treatment. No patients had hemorrhagic cystitis.

Conclusion: 14 day CIV ifosfamide is a viable option for advanced sarcomas with a CBR of 68.1%. The median PFS was 14 weeks. The data in this retrospective study has fostered a prospective evaluation of CIV ifosfamide in advanced sarcomas.

Keywords: Sarcoma; Ifosfamide; Chemotherapy; Metastasis

Abbreviations

ANC: Absolute Neutrophil Count; CBR: Clinical Benefit Rate; CHF: Congestive Heart Failure; CIV: Continuous Intravenous Infusion; ESMO: European Society for Medical Oncology; LMS: Leiomyosarcoma; MESNA: 2-Mercaptoethane Sulfonate Na; MPNST: Malignant Peripheral Nerve Sheath Tumor; NCCN: National Comprehensive Cancer Networks; PFS: Progression Free Survival; RR: Response Rate; STS: Soft Tissue Sarcoma

Introduction

Sarcomas are a group of roughly 80 rare connective tissue neoplasms of mesenchymal origin that are broadly classified as originating from soft tissues or bones and total about 15000 cases per year [1,2]. Standard management is usually determined by multidisciplinary teams at sarcoma referral centers and from ESMO and NCCN guidelines. For metastatic disease and locally advanced tumors for which local control is not an option, chemotherapy and targeted agents are used.

Historically, the most commonly used chemotherapies include doxorubicin, the oxazaphosphorines ifosfamide and cyclophosphamide, dacarbazine, vincristine, etoposide, topoisomerase inhibitors and a combination of gemcitabine and taxotere. As the molecular underpinnings of these diseases have become better understood, targeted agents such as pazopanib, imatinib, and denosumab have entered the clinic [3-5]. Yet, it is still not clear what is the best dose or schedule for many chemotherapies particularly ifosfamide. It is felt that maximum tolerated dose and the dose intensity for most cytotoxic agents administered by bolus and infusional schedules is unpredictable and variable and is influenced by the infusion duration and the interval between treatment cycles [6]. In addition, myelotoxicity was a limiting factor, but, in the modern era of chemotherapy, white blood cell growth factors have improved our ability to deliver dose dense chemotherapy.

Ifosfamide has been given as bolus as well as continuous intravenous [CIV] dosing ranging from 5-18g/m^2/cycle [7]. These doses have been administered most commonly over 3-4 days. Moreover, it has been demonstrated preclinically and clinically that ifosfamide has a steep dose response curve with the best responses noted over 9g/m^2, and that patients may re-respond to high dose ifosfamide if they progressed on a lower dose [8,9]. Furthermore,

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Table 1: Patients' Characteristics.

Patient Characteristics	
Patients	47
Median Age	49 (12-85)
Gender	
Male	19 (40%)
Female	28 (60%)
Histologic Subtypes	
Leiomyosarcoma	15
HGUPS/MFH	6
Synovial Sarcoma	6
Osteosarcoma	4
Rhabdomyosarcoma	4
Liposarcoma	3
Others	9
Previous Lines of Chemotherapy	
0	2
1	10
2	18
3	3
4	5
>4	9
Previous Ifosfamide	
Yes	16
No	31

Donehower has noted 'one of the important variables to be explored in clinical cancer chemotherapy is the duration of time that the exposure to malignant cells to the actions of neoplastic drugs can be maintained [10]. In addition, because of the logistics and cost of giving high dose ifosfamide in the hospital or from long clinic infusion encounters, as well as the toxicity from bolus dosing, Lokich *et. al.* [11] investigated administering a 14 day CIV ifosfamide regimen. Two subsequent studies have examined the safety and efficacy of ambulatory 14-day continuous infusional ifosfamide in 14 pediatric and 35 adult sarcoma patients [12,13]. In this study, we add to the literature that 14 day continuous infusional ifosfamide is safe and effective in a wide range of soft tissue and bony sarcomas, even in patients who were previously treated with ifosfamide. Herein, we present the results of 47 patients who were treated with this regimen.

Materials and Methods

Patients

Patient data was collected from 35 patients treated retrospectively and 12 patients treated prospectively at the Sarcoma Oncology Center with 14 day continuous infusion ifosfamide from 8/30/2010 to 7/28/2014. Patient characteristics are included in Table 1. The study of the patients in the prospective group was approved by the Western IRB. Patients were required to have a histologic diagnosis of locally advanced/metastatic soft tissue or bony sarcoma that was not amenable to control with surgery or radiation therapy. They were required to have adequate bone marrow [Absolute neutrophil count >1500, Hemoglobin>8g/dL, Platelets>100 x 10^3/μL], renal function [CrCl<1.5xUpper limit of normal] and performance status [ECOG <2] for whom the investigator decided ifosfamide was a reasonable choice. There was no limit to the number of previous lines of therapy.

Table 2: Response to Ifosfamide by Histology.

Best Response	LMS	HGUPS	Synovial Sarcoma	Osteo	Other
CR	0/15	1/6	0/6	0/4	0/16
PR	4/15	0/6	1/6	1/4	3/16
SD	5/15	3/6	5/6	2/4	7/16
PD	5/15	2/6	0/6	1/4	4/16
Not Evaluable	1/15	0/6	0/6	0/4	2/16

Table 3: 14 Day CIV Ifosfamide Comparison.

14 Day CIV Ifosfamide Studies			
STUDY	**RR**	**CBR**	**Median PFS (weeks)**
Meazza et al.	5/14 = 35.7%	64.3%	12.0 (8-76)
Martin-Liberal et al.	7/35 = 20.0%	48.6%	16.8 (8-25)
Singh et al.	10/47 = 21.2%	68.1%	14.0 (2-110)
All 3 studies	22/96 = 22.9%	57.4%	

Table 4: Grade 3,4 Toxicities.

Grade 3,4 Toxicities	
Neutropenia	60.0%
Anemia	23.4%
Thrombocytopenia	8.5%
Neurologic	10.6%
Nausea	2.1%

Ifosfamide treatment

Ifosfamide was administered in conjunction with MESNA to ameliorate urothelial toxicity at 1g/m2/day of ifosfamide (and 1g/m2 of MESNA) via a continuous infusion pump over 14 consecutive days in 28 day cycles. Pumps were loaded with mixtures of ifosfamide and MESNA and refilled every 3-4 days depending on the starting day of infusion. Patients were alkalinized with oral bicarbonate tablets, instructed to drink at least 1.5L water per day, but were given supplemental IV hydration on pump change days as well as supplemental magnesium and potassium as necessary. All patients were given antiemetics and growth factor support with peg-filgrastim, filgrastim or sargramostim. There was no limit to the number of cycles, given that there was no CNS, renal or hematologic adverse event to discontinue treatment. Dosing of ifosfamide was adjusted to patient tolerance and toxicity. Myelosuppression, renal dysfunction and CNS toxicity was recorded.

Efficacy evaluation

All patients included in this analysis had measurable disease. CT, MRI or PET imaging was used to response assessment and response was determined via RECIST 1.1 parameters. Progression Free Survival [PFS] was determined from the date of starting treatment to the date of objective disease progression or death. Patients who were alive and still undergoing treatment were censored at their last follow up date. The median PFS was calculated using Kaplan Meier Analysis.

Results and Discussion

47 patients received 14 day CIV ifosfamide from 2010 to 2014. There were slightly more females than males: 60% to 40% and the median age of patients with 49. Both patients with soft tissue and bony sarcomas were treated. The most common histologies were high grade leiomyosarcoma [n=15], synovial sarcoma [n=6], HGUPS [n=6], osteosarcoma [n=4] and rhabdomyosarcoma [n=4] (Table 1). A full list of histologies is included in Supplemental Table 1. This was a heavily pretreated population of patients as 74 % had 2 or more lines of previous therapy including chemotherapy, targeted therapy and investigational agents. 34%were previously treated with ifosfamide.

Of grade 3/4 hematologic toxicities, 60% had neutropenia, 23.4% had anemia and 8.5% had thrombocytopenia (Table 4). Of grade 3/4 non-hematologic toxicities, 5 patients (10.6%) had neurologic toxicity, 1 had nausea/vomiting, 1 had CHF and 1 patient died while receiving treatment. No patients had hemorrhagic cystitis (Table 2). Of the neurologic adverse events, 3 patients were female and 2 were male. Overall, this toxicity level was much greater than that reported by Meazza *et al.*, though prolonged neutropenia delaying infusions and neutropenic fevers were noted in that pediatric population. Our reported grade 3/4 hematologic toxicity rate was also much higher than reported by Martin-Liberal *et al.*, though 65% of patients in that study received ifosfamide as front line chemotherapy. However, the toxicity rates noted are similar to other studies of high dose ifosfamide in adult populations given via bolus/CIV [14,15].

In this cohort of patients, 1/47 patients had a CR (2%), 9/47 had a PR (19.1%) and the CBR (CR+PR+SD) was 68.1%. The median PFS was 14 weeks (range: 2-120 weeks). The patient who experienced a clinical CR with CIV ifosfamide had HGUPS and was treatment naive. He was not considered to be a surgical candidate and as such was started on CIV ifosfamide. After his impressive response, the patient refused additional chemotherapy. He was seen in consultation at outside institutions and eventually had a relapse requiring surgery; however, his response was censored at the time he elected to stop chemotherapy. 4/15 patients with LMS, 1/6 with synovial sarcoma, 1/4 with osteosarcoma and 3/16 with other diagnoses (hemangioendothelioma, angiosarcoma, MPNST) had a PR (Table 2). The response rate of the cohort in this study of a wide group of soft tissue and bony sarcomas is similar to the response rate noted by Martin-Liberal *et al.*, though that study contained a high proportion of dedifferentiated liposarcomas patients. Meazza *et al.* noted a higher response rate for a pediatric population, though this study contained much fewer patients (Table 3). Overall, the CBR was similar between the 3 studies. The PFS rates were also very similar, though Martin-Liberal *et al.* noted a 2.8 week improvement in PFS; this however may be due to the more indolent course of dedifferentiated liposarcomas compared to other high grade sarcomas.

It was noted that of the 6 synovial sarcoma patients in this study, 1 had a PR and the other 5 patients all had stable disease. Three of these six patients were previously treated with ifosfamide (1 PR and 2 SD) and the other 3 patients had received other forms of chemotherapy. The median PFS was 25.5 weeks (Range: 6-71 weeks). This is in keeping with the noted response of synovial sarcoma to ifosfamide based regimens [16]. Of the 15 LMS patients on study, 4 had a PR and 5 had stable disease with a median PFS of 12 weeks. Interestingly, one patient with LMS went 110 weeks without progression of her disease, though she did require ifosfamide dose reductions.

16 patients were previously treated with an ifosfamide based regimen. 4/16 had a PR (25%) and another 7 had stable disease (43.5%) for a CBR (68.5%). 4 patients had progressive disease and one could not be evaluated as scans were pending. The 4 patients who had a PR had synovial sarcoma, osteosarcoma, MPNST and LMS.

The PFS in the ifosfamide pretreated population was 25 weeks and the PFS in the ifosfamide naïve population was 12.5 weeks. It should be noted that many patients in the pretreated population received ifosfamide in the neo/adjuvant setting and also stopped receiving ifosfamide after 6 cycles of the AIM regimen in some cases and may not have been true ifosfamide failures. Also, since this is alargely retrospective study, selection bias may have influenced the large PFS differences seen in the ifosfamide naïve and pretreated populations. The investigators may have chosen fitter patients and histologies that were known to be more ifosfamide responsive.

Ifosfamide is one of the most active drugs in sarcoma and yet the optimal administration schedule has not been defined. It is clear that ifosfamide, when constituted with MESNA or other chemotherapies is stable for 14 day continuous administration and multiple studies have demonstrated the practical feasibility of this approach [17,18]. In this cohort of patients, we noted that ifosfamide given as a 14 day CIV is active against a wide variety of sarcomas with comparable RR and CBR to other studies with high dose ifosfamide. Moreover, it is clear that patients who were previously treated with ifosfamide may re-respond to this medication as 25% of patients previously treated with ifosfamide responded to this medication and the median PFS in this group was 25 weeks, further confirming a clinical observation noted by Palumbo *et al.* and references therein [8].

Conclusion

14 day CIV ifosfamide offers the theoretical advantage of metronomic dosing and can be given in an ambulatory setting and produces responses in heavily pretreated bone and soft tissue sarcoma patients. Patients who were previously treated with ifosfamide can still re-respond to this chemotherapy and derive disease control. Side effects of myelosuppression are manageable.

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