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Research Article

Trofosfamide and Etoposide - A Well Tolerated Palliative Treatment for Adults with Advanced Soft Tissue Sarcoma: A Single Center Experience

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Abbreviations TE: Trofosfamide and Etoposide; GIST: Gastrointestinal Stromal Tumor; STS: Soft Tissue Sarcoma; CR: Complete Remission; PR: Partial Remission; PD: Progressive Disease; SD: Stable Disease; RECIST: Response Evaluation Criteria in Solid Tumors; NCI: National Cancer Institute; CTCAE: Common Terminology Criteria for Adverse Events; MDS: Myelo Dysplastic Syndrome; EPO: Erythropoietin; G-CSF: Granulocyte Colony Stimulating Factor

Abstract

Background: Patients with a metastatic or locally advanced Soft Tissue Sarcoma (STS) are normally treated with chemotherapy. However, pretreated or vulnerable patients with comorbidities may have difficulties tolerating the intensive intravenous standard regimens. Trofosfomide, a peroral prodrug to ifosfamide, has been described to have promising effects in the treatment of STS. For childhood STS the combination of trofosfamide and etoposide has been used as maintenance therapy, but its utility in the treatment of adult STS has yet to be described.

Methods: A retrospective single center experience comprising of 69 adult patients with advanced STS, treated with Trofosfamide and Etoposide in combination (TE), is presented. The medical records, including pathology and radiology reports, of all patients who initiated TE between May 2002 and September 2015 were reviewed. We present data on duration of treatment, best radiological response and reason for ending treatment and side-effects. The treatment schedule consisted of oral trofosfamide 100 mg (total dose) twice a day from day 1-10, and oral etoposide 50 mg (total dose) twice a day from day 1-10, with a cycle length of 21 days.

Results: Among the 69 patients, the median treatment time was 103 days. A treatment time longer than 90 days were noted for 55.1%, and more than 180 days for 31.9 %. Patients with synovial sarcoma and well-differentiated liposarcoma had the longest treatment times. Long treatment times were also noted in patients with other STS histologies. The treatment was well tolerated, regardless of patient age. Hematological toxicities however lead to dose-reductions and supportive measures in more than half of the cases. Three patients were diagnosed with MDS after long treatment times.

Conclusions: The combination of trofosfamide and etoposide is shown to be an effective and well tolerated treatment for adult patients with advanced STS of different histiotypes. TE is a good treatment option for heavily pretreated or vulnerable patients, e.g. caused by comorbidities. The risk for developing secondary cancer after treatment with TE should be considered.

Introduction

In patients with metastatic or non resectable locally advanced non-GIST Soft Tissue Sarcoma (STS), chemotherapy is the main treatment option. Despite of emerging treatment alternatives [1,2] and increased knowledge in histology-driven treatment [3-5], the 5-year survival of patients with metastatic disease is only 8-20% when chemotherapy is combined with surgery [6-9]. The median overall survival for a non-pediatric patient with metastatic STS is reported to be 12-18 months [10,11].The prognosis for elderly patients is even worse [11].

The chemotherapeutic drugs and regimens that are widely used to treat metastatic STS are linked to many side-effects. Tolerance may be problematic especially in patients with co-morbidities, and those already heavily treated for their sarcomas.

Treatment with single oral trofosfamide, an alkylating agent, has earlier been described as well-tolerated and active in adult patients with STS [12-15]. Treatment with single oral etoposide has shown objective responses in childhood STS [16], but low or no efficacy in studies treating adult STS [17,18].

In the CWS-96-protocol, the combination of oral Trofosfamide and Etoposide (TE) was part of the oral maintenance in children with advanced STS. It was reported as a promising option [19].The TE combination has however not yet been described as a treatment used in adult patients with advanced STS. Based on experiences of patients responding after the addition of etoposide to trofosfamide at our department, we have used this combination in several cases during the last 15 years. Here we present our single center experience of the combination.

Materials and methods

All patients diagnosed with STS that initiated treatment with TE from May 2002 to September 2015 at our center, were identified and included in the review. Data were collected from their medical records including pathology and radiology reports. Even if this is not a prospective clinical trial, any potential remission (complete remission, CR, and partial response, PR) had to be verified according to RECIST 1.1 [20] by an experienced radiologist. However, it was not considered meaningful to make a comprehensive similar review to differ stable disease, including all minor responses, from true progressive disease in this kind of retrospective review. Instead, clinically convincing overall progression was considered as Progressive Disease (PD). Other outcomes, e.g. minor regression and mixed response, were regarded as Stable Disease (SD). However, data on radiologically or clinically observed minor regressions were also noted separately.

The treatment schedule consisted of oral trofosfamide 100 mg (total dose) twice a day from day 1-10, and oral etoposide 50 mg (total dose) twice a day from day 1-10, with a cycle length of 21 days. If myelosuppression occurred, subsequent cycles were delayed until hematological recovery. If dose reduction was necessary, the number of treatment days, and not the daily dose, was reduced in each cycle.

Collected data for all patients includes gender, age, histological subtype, tumor presentation, treatment indication, previous and further treatments, time on treatment, radiological outcome, noted toxicities of any grade, management of toxicities, dose adjustments and reason for ending treatment. The National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) were used to classify adverse events [21].

Results

Sixty-nine patients were identified (40 M, 29 F), with a median age of 64 years, Table 1. Fifty-nine patients had metastatic disease and the remaining had locally advanced and/or inoperable disease.

Fifty-five patients had STS-related symptoms at the start of TE. The other patients were asymptomatic, but had progressive disease, considered to constitute an imminent threat to the patients´ well-being. Thus, no asymptomatic non-progressive patients were included and no patients were kept on treatment without a meaningful outcome. This also includes the WD liposarcomas as described below.

Leiomyosarcoma was the most frequent histological subtype, followed by Undifferentiated Pleomorphic Sarcoma (UPS). Fifty-nine patients had highly malignant tumors. All cases had been histologically diagnosed according to the World Health Organization Classification of Tumors [22] by specialized sarcoma pathologists at our center. The histological grade was determined according to the French three-tired, or the Scandinavian Sarcoma Group four-tired grading system. Sixteen patients had been considered primarily inoperable, and their histological diagnoses were based on core needle biopsies.

Fifty-six patients had been treated with at least one earlier line of chemotherapy with adjuvant or palliative intention. In 13 patients TE was the first line of treatment. Five patients had progressive disease on treatment with single trofosfamide treatment at the start, but after the addition of etoposide two patients (one with synovial sarcoma, one with solitary fibrous tumor) reached minor responses. Five patients were in the medical records described as having excellent responses, and were radiologically reviewed. Two cases with PR according to RECIST were confirmed (Table 1).

All patients had a radiological examination within maximum 4 weeks before initiating treatment with TE, making objective evaluation possible. The first evaluation was made after 2 to 3 cycles. If treatment continuation was determined, further evaluations were made every second or third month. TE was continued as long as the patient benefitted from the treatment, this included having acceptable side-effects. In one case, a patient with slight progression of disease after 3 cycles declared relief of STS-related symptoms, and proceeded treatment with two more cycles. All other patients with unambiguous progressive disease at evaluation discontinued treatment (Figure 1).

Table 1: Clinical characteristics.

Patients		69
Sex	Male:Female	40:29
Age at start of TE	Median (range)	64 (23-88)
	≥ 70 years	28
Histology	Leiomyosarcoma	20
	UPS	10
	Spindle-shaped STS NOS	10
	Synovial sarcoma	9
	Well-differentiated liposarcoma	4
	Liposarcoma, other	4
	Myxofibrosarcoma	3
	Angiosarcoma	2
	Other	7
Tumour malignancy grade	High	59
	Low-intermediate	10
Disease	Locally advanced / inoperable	10
	Metastatic	59
	Metastatic-single organ	23
	Metastatic-multiple organs	36
Sites of metastases	Lung	52
	Bone	15
	Lymph nodes	13
	Liver	11
	CNS	6
Previous chemotherapy		56
TE-line of treatment	1 st	13
	2 nd	23
	3 rd	21
	4 th	9
	5 th	1
	6 th	2
Further treatment after TE		23

Previous chemotherapy and lines of treatment includes adjuvant treatments where applicable.

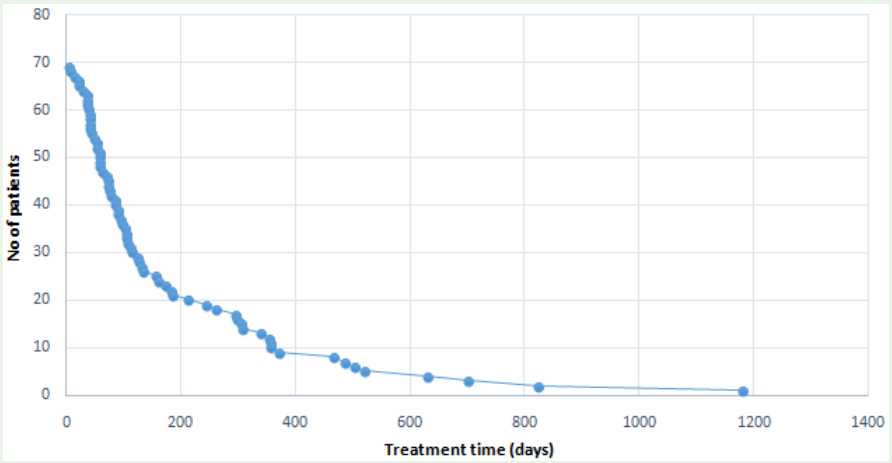


Figure 1: Treatment time, all patients.

Table 2: Median treatment time and best response according to histological subtype.

Histological subtype	No of patients	Median treatment time, days (range)	PR n (%)	SD n (%)	PD n (%)	Not evaluated n (%)
Leiomyosarcoma	20	117 (14-703)	0	12	5	3
UPS	10	81.5 (22-358)	1	5	3	1
Spindle-shaped STS NOS	10	97.5 (7-371)	0	7	2	1
Synovial sarcoma	9	308 (37-825)	1	5	3	0
Well-differentiated sclerosing liposarcoma	4	319 (95-1182+)	0	3	1	0
Other	16	82 (5-486)	0	8	5	3
All subtypes	69	103 (5-1182+)	2(2.9)	40 (58.0)	19 (27.5)	8(11.6)

Blood test, which included hemoglobin, leukocytes, neutrophils and thrombocytes, were controlled weekly, and the results were noted in the medical records.

When the final data was collected in April 2016, one patient was still undergoing treatment with TE.

The median treatment time for all patients was 103 days (range 5-1182+). Thirty-eight patients (55.1%) were treated for more than 90 days, and 22 (31.9%) patients were treated for more than 180 days, Figure 1.

Patients with well-differentiated liposarcoma (retroperitoneal or funicle location) had the longest median treatment time of 319 days, followed by synovial sarcoma which had a median of 308 days. However, in different histological subtypes there were patients with treatment time that exceeded 200 days, Table 2.

Median treatment times were not considerably different between patients who were <70 years at the start of treatment (112 days, range 5-1182+) and patients ≥ 70 years (93.5 days, range 14-631). The oldest patient was an 88 year old male with retroperitoneal leiomyosarcoma, who had progressed before start of TE and whose treatment lasted for 631 days with a long period of SD.

The median treatment time was longer (175 days, range 54-1182+) for patients receiving the treatment as first line of chemotherapy (Table 3). Median treatment time gradually declined with increasing line of treatment. Three patients had TE as fifth or sixth line of treatment, and none of them experienced any benefit of the treatment. In the group of patients receiving TE as fourth line the longest treatment time was 307 days.

The two cases reaching PR had treatment times of 358 (Figure 2a,b) and 521 (Figure 3a,b) days, respectively. Forty patients with SD as best outcome had a median treatment time of 179.5 days. Thirteen patients with SD had a radiological minor regression after convincing progression at start. Nineteen patients had obvious progressive diseases at the first evaluation, and their median treatment time was 53 days. Eight patients were never evaluated, due to early deterioration and/or death, and their median time of treatment was also the shortest, 30.5 days.

Figure 2 demonstrates chest X-rays of a 78 year old woman with undifferentiated pleomorphic sarcoma, which was metastatic at time of diagnosis. Due to comorbidities (hypertonia, diabetes) she received TE as a 1st line treatment. **a** Chest X-ray at start of TE showing multiple, largepulmonary metastases. **b** Chest X-ray after 4 months

Table 3: Median treatment time according to line of treatment.

Line of treatment	No of patients	Median treatment time, days (range)
1	13	175 (54-1182+)
2	23	103 (22-521)
3	21	87 (7-825)
4	9	65 (5-307)
5	1	42
6	2	41 (37-45)

of TE showing PR according to RECIST. The patient described relief of symptoms and tolerated TE well. Total treatment time 358 days.

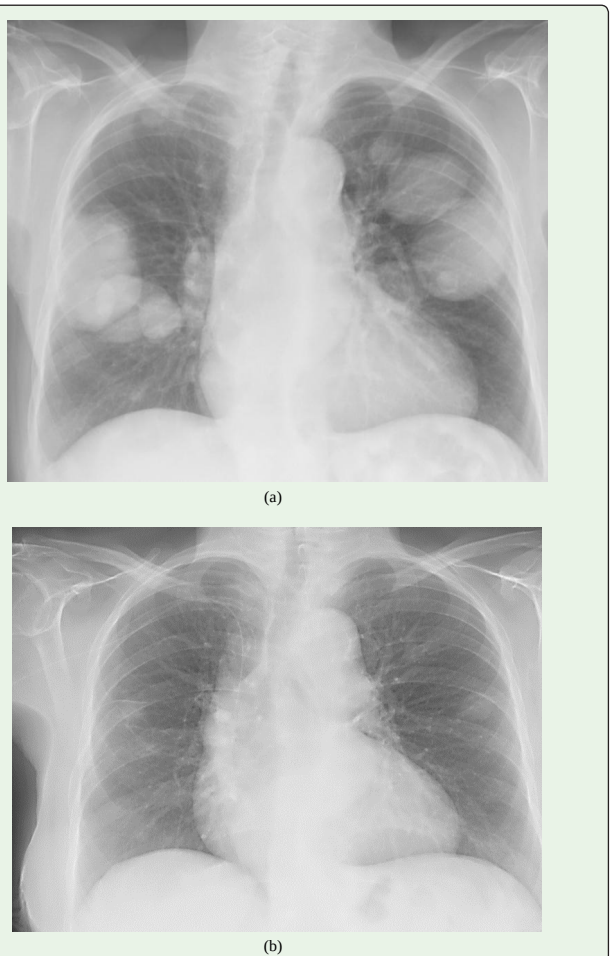
Figure 3 Shows CT images of a 27 year old male with synovial sarcoma with metastases in the lung and bones. At diagnosis of a lower extremity synovial sarcoma 3 years earlier, he had received postoperative radiotherapy and adjuvant chemotherapy (doxorubicin and ifosfamide). When metastases were found the patient refused intravenous chemotherapy. aCT scan at start of TE showing a large pulmonary/pleural metastasis. bCT scan after 12 months of TE showing PR according to RECIST. The patient described symptomatic relief and tolerated TE well. Total treatment time was 521 days.

The patient with the longest treatment time, which surpassed 1182 days (still on-going April 2016), was a 69 year old male with a well-differentiated retroperitoneal liposarcoma. The disease was progressive before the start of treatment, but after the initial treatment minor regression and symptom relief was seen, and the disease had been stable since more than 2 years in April 2016.

The second-longest treatment time was 825 days. This was achieved by a 35 year old woman with lung-metastases from a synovial sarcoma who had received doxorubicin-ifosfamide as 1st line and high dose ifosfamide as 2nd line. High dose ifosfamide was ended due to intolerance, and during treatment with TE the patient had a long period of disease under control which even included a minor regression.

Toxicities were mainly hematological, and different grades of anemia, leukopenia and thrombocytopenia were common. However, many pretreated patients had reduced blood-counts at the start of treatment. Nine patients ended the treatment due to intolerance; 7 because of hematological toxicity, which was often combined with fatigue, 1 heavily pretreated patient due to progressive peripheral neuropathy (CTCAE grade 2), and 1 patient with retroperitoneal tumour due to increasing gastrointestinal problems. Nine patients (10 events) were hospitalized due to side-effects of the treatment. The reason for dose-reduction in 37 patients was in most cases hematological toxicity. Two patients had total alopecia. In general, however, hair loss was limited. A summary of the management of toxicities are shown in table 4.

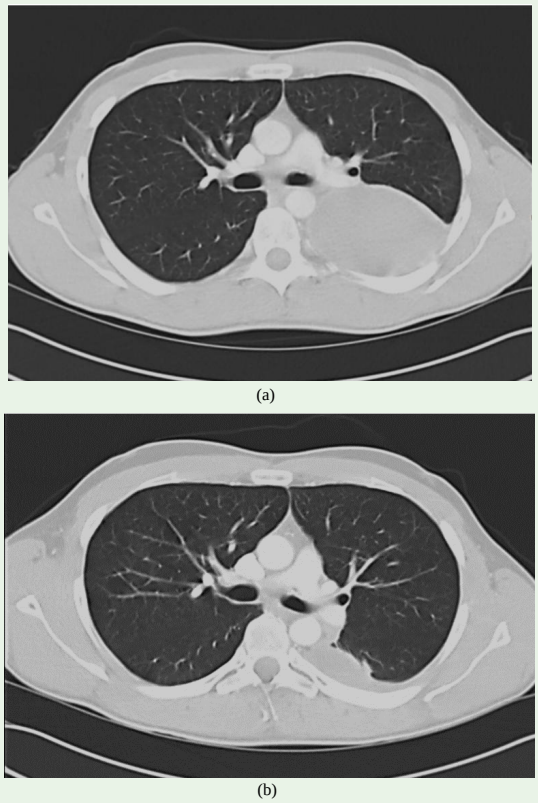
Fifty-two patients ended treatment due to PD or rapid deterioration. Nine patients ended treatment due to intolerance, without PD. One patient died due to sepsis, with a normal White Blood Cell count. Three patients ended TE due to intensification of treatment, i.e., they were considered to manage another treatment that could be more beneficial. Four patients ended treatment after the diagnosis of another malignancy; 3 developed Myelo Dysplastic Syndrome (MDS), and 1 developed lung cancer. The patients diagnosed with MDS had been on treatment with TE for 371, 631 and 703 days, respectively. One of the patients had received adjuvant doxorubicin–ifosfamide two years earlier; the two other patients



(a)

(b)

Figure 2: Radiological evaluation in a patient with undifferentiated pleomorphic sarcoma.



(a)

(b)

Figure 3: Radiological evaluation in a patient with synovial sarcoma.

Table 4: Management of toxicity.

Action taken	No of patients
Treatment discontinued	9
Dose-reduction	37
Blood-transfusion(-s)	39
EPO	8
G-CSF	8
Platelet-transfusion	2
Hospitalization due to febrile neutropenia	8 (9 events)
Hospitalization due to nausea/dehydration	1
Antiemetics	17
Anti-diarrhoeal drugs	3

EPO: Erythropoietin, G-CSF: Granulocyte Colony Stimulating Factor

had TE as 1st line of chemotherapy. One of these had a Li-Fraumeni Syndrome, but was chemotherapy-naïve.

No immediate treatment related deaths were identified.

Twenty-three patients received further treatment after TE, most often with tyrosine kinase receptor inhibitors.

Discussion

We present a retrospectively conducted single center experience of a palliative treatment, given to adult patients with generalized or locally advanced STS. Treatment time and best radiological response has been presented. The treatment was ended in the case of disease progression, or if the patient was not considered to have derived benefit from the treatment. The majority of patients ended their treatment due to disease progression or intolerance. In vulnerable or heavily pretreated adult patients with advanced STS the combination of trofosfamide and etoposide offers a treatment option for a substantial number of patients.

We found patients <70 years of age, patients ≥70 years and patients with up to 3 earlier lines of treatment who had been treated under a long period of time.

Patients with synovial sarcoma seem to especially benefit from the treatment. This finding is not surprising as the histology subgroup is well-known to be chemo-sensitive, especially to ifosfamide, a drug closely related to trofosfamide. However longer periods of stabilization and minor regressions of disease is also seen in patients with e.g., well-differentiated retroperitoneal liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma and meningeal sarcoma (one patient).

Hematological side effects are frequent, but are easily manageable. There are other side effects, but these are often limited. The treatment does not require in-patient hospital care, and the cost of the drugs, that have been out on the market for many years, are reasonably low compared to the cost of many new anticancer drugs.

Conclusion

The combination treatment schedule with Trofosfamide and Etoposide (TE) given orally has not yet been reported as a treatment option for adult patients with advanced STS. Our experience suggests that the regimen is a safe and most often well-tolerated treatment. This treatment may provide a benefit in different histological subtypes of STS, both for younger and older adults. However, there appears to be a certain risk to develop MDS.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to potential patient identifiers (rare diseases in combination with age, sex and place of treatment) in the datasets. The datasets are available from the corresponding author on reasonable request.

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