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THE RESULTS OF COMBINATION OF IFOSFAMID AND LOCOREGIONAL HYPERTHERMIA (EHY 2000) IN PATIENTS WITH ADVANCED ABDOMINAL SOFT-TISSUE SARCOMA AFTER RELAPSE OF FIRST LINE CHEMOTHERAPY*

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Abstract. From 2003 to 2011, 24 patients with advanced soft-tissue sarcoma with high-risk pretreated using first line chemotherapy with doxorubicin and recurrence disease were treated with chemotherapy (ifosfamide 3000mg/sqm, day 1–3) and locoregional hyperthermia (1 hour application with temperature between 41.5°C and 42°C, 3 days/week). The purpose was to evaluate the efficacy and safety of chemotherapy combined with locoregional non-invasive hyperthermia for local tumor control in patients with retroperitoneal or visceral advanced soft tissue sarcomas. From 24 patients, 18 patients have had an evaluable response on CT scan using RECIST 1.0 (stable disease 8 patients for 4 months and 1 patients for 1 month, partial response 8 patients for 4 months, progression disease for 1 patient). The response was mainly on local tumor site. The side effects were correlated only with chemotherapy (neutropenia grade III 40%, grade 4 20%, trombocytopenia 2%, anemia grade III 10%, neurologic toxicity 9%). No toxicity was correlated with hyperthermia treatment.

Key words: soft-tissue sarcoma, chemotherapy, locoregional hyperthermia.

1. INTRODUCTION

Soft tissue sarcoma prognosis factors are high grade histology results, large tumor size (>5cm) and deep localization [1]. If median overall survival for the

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patients with extremity STS is 33 months, the patients with retroperitoneal STS have reported an overall survival between 9 and 20 months [2, 3]. It was proven that retroperitoneal or visceral sites are an additional poor prognostic factor, independent of other factors like grade, tumor size and recurrence [4].

After radical excision, five-year survival rates of undifferentiated retroperitoneal and visceral STS were reported to be as low as 16% [5]. In a strategy to improve local tumor control, a multimodal treatment including regional hyperthermia (RHT) seemes attractive to be explored in this high-risk patient population.

The rationale for the combination of cytotoxic drugs with hyperthermia in the treatment of high-risk STS (HR-STS) is based on experimental evidence that heat exposure increases tumor cells death rate by direct thermal cytotoxicity and is able to sensitize perfused tumor tissue towards chemotherapy in a synergistic manner [6].

The primary endpoint of this trial was represented by the response rate of combined chemotherapy (ifosfamide) with loco-regional hyperthermia for patients with metastatic soft tissue sarcoma with progression after first line chemotherapy with doxorubicin. The response rate can be an indicator for efficacy of treatment if in a small group of patients, there is a response rate greater than 40% at 3 months for the second line treatment [7, 8].

Secondary objectives were: safety evaluation of the combined chemotherapy-hyperthermia treatment and evaluation of progression free survival.

Patients and methods. Between 2003 and 2011, a total of 24 patients diagnosed with metastatic soft tissue sarcoma and progressive disease after doxorubicin treatment were enrolled in the trial. STS was localized in abdominal and retroperitoneal regions, with positive histopathology and no cKIT mutations. Relapsed disease after treatment was confirmed by CT scan evaluation with RECIST 1.0 and after signing the informed consent. The treatment from this protocol with ifosfamide and locoregional hyperthermia was approved by the local ethics committee of the Euroclinic Center of Oncology.

Patients' characteristics. The criteria for inclusion in this study were the following: a minimum of 2 points at ECOG performance status evaluation, no major cardiac disease, adequate bone marrow, good hepatic and renal functions (bilirubin less than 2 x ULN), retroperitoneal or abdominal soft-tissue sarcoma with positive histopathology and no c-KIT mutations. Every patient have received minimum 2 cycles of doxorubicin before progression of the disease. The main characteristics of the patients are presented in Table 1.

Table 1

Characteristic	Nr. of patients
Performance status	
ECOG 2	4
ECOG 3	14
Site of metastasis	
Lung	8
Liver	11
Bone	7
Hystopathologic Type	
Fibrosarcoma	5
Mixofibrosarcoma	2
Synovial sarcoma	3
Leiomyosarcoma	3
Epithelioid Sarcoma	2
Angiosarcoma	3

Chemotherapy regimen. The chemotherapy protocol comprised of ifosfamide given 3 consecutive days (ifosfamide 3000 mg/sqm, day 1–3) and uroprotection (Mesnum), repeated at 21 days (Fig.10). As premedication, the following were administered: Ondansetron 8 mg po/IV q 8 h × 3 doses (first dose pre-chemotherapy), dexamethasone 8 mg po/IV pre-chemotherapy, then 4 mg po/IV q 12 h × 10 doses, Lorazepam 1 mg SL q 4–6 h prn nausea, sleep or restlessness, Prochlorperazine 10 mg po/IV q 4–6 h prn nausea and vomiting.

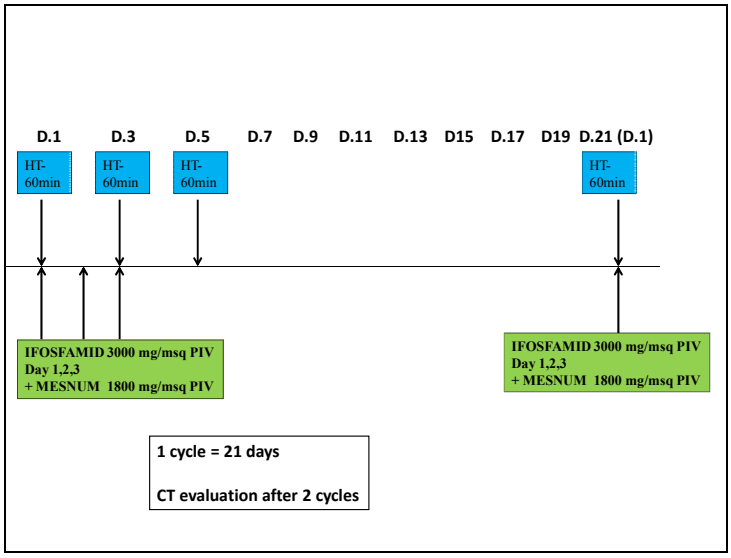

Fig. 1 – The schedule of treatment (chemotherapy + hyperthermia).

Locoregional non-invasive hyperthermia. The treatment with locoregional hyperthermia was performed 3 days/week with 1 hour applications between 41.5°C and 42°C, repeated at 21 days, until progression.

Toxicity evaluation. Adverse events were collected after every cycle and were reported after CTC-AE system.

Treatment Evaluation. The response of the treatment (chemotherapy with hyperthermia) was evaluated with CT evaluation (after every 2 cycles of the treatment) using RECIST system.

2. RESULTS

Treatment delivery and toxicities. A total of 76 chemotherapy cycles were administered to 18 patients. Locoregional hyperthermia was administered concomitently with chemotherapy. Chemotherapy was interrupted when disease progression was demonstrated (after CT evaluation - RECIST system) or when the performance status of the patient was higher than ECOG 3 (clinical progression of the disease). Four patients had their treatment stopped due to low performance status.

3. TOXICITY ASSESSMENT

Chemotherapy toxicity. Chemotherapy related toxicity was assessed after every cycle and was related to CTC-AE criteria. All toxicities were transitory and were resolved without sequelae. There were 3 patients with dose reduction due to grade IV neutropenia.

Toxicity	[%] of patients
Hematologic	
neutropenia grade III	40
neutropenia grade IV	20
anemia grade III	10
thrombopenia grade III	2
Non-hematologic	
neurologic toxicity	9

Hyperthermia associated toxicity. There were some adverse effects related to hyperthermic treatment: discomfort related with bolus pressure in 4 patients (grade II – CTC AE criteria) and pain related with position in 3 patients (grade II – CTC AE criteria).

Combined treatment toxicity (chemo + locoregional hyperthermia) was within normal values, mostly related to chemotherapy, demonstrating that association between hyperthermia and chemotherapy is safe.

Response. The primary endpoint was represented by response rate of chemotherapy (ifosfamide) combined with loco-regional hyperthermia. For this purpose, the Simon two stage design was utilised. According to a Van Glabbekea study [7], if soft tissue sarcomas treatment has a response rate greater than 40% at 3 months, it becomes a treatment efficacy indicator; less than 20% is an indicator of non-efficacy. In this trial, out of 18 patients, 8 (44%) had stable disease 4 months, 1 patient (6%) had stable disease 1 months , 8 patients (44%) with partial response 4 months and 1 patient (6%) with progression disease. In these conditions, there is a rate of 44% for partial response and this indicates a necessity to continue patient enrollment.

For the progression free survival period, this was calculated and the median was 4.7 months (Fig. 2).

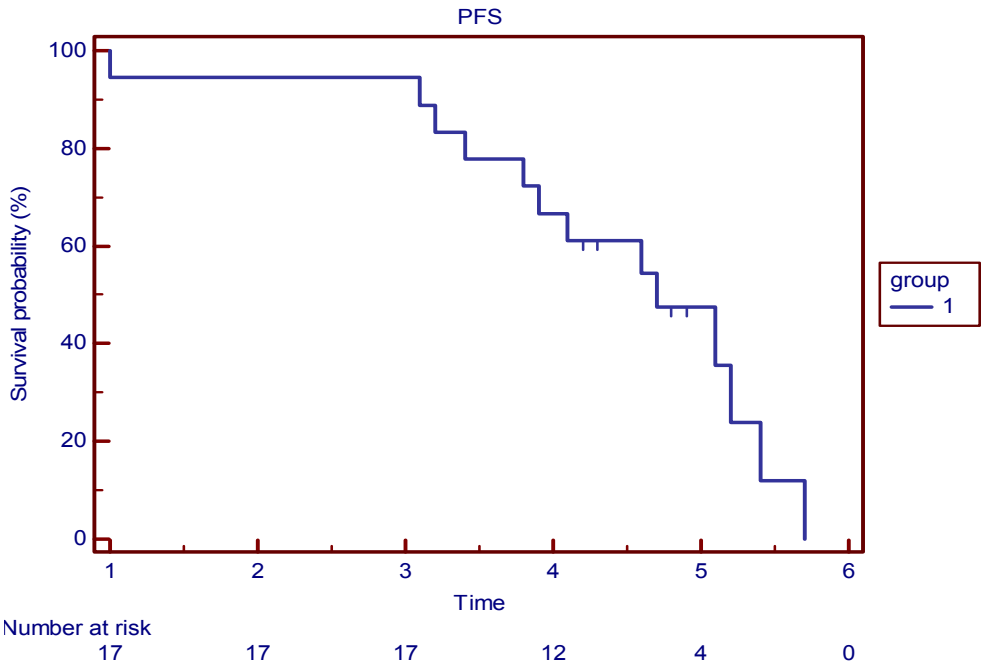

Fig. 2 – Progression free survival for 18 patients enrolled.

Treatment safety was evaluated after every cycle and the conclusion was that the treatment adverse events were only related with chemotherapy.

4. DISCUSSION

For phase II trials, the most popular statistical design is the two steps optimal and minimax designs proposed by Simon [9]. Fleming [10] has also proposed a single step design based on a similar hypothesis, but not relevant for this study. The design proposed by Gehan [11] is sometimes used in early phase II trials, when a decision rule is not crucial.

Results obtained in this study of 44% rate of response (partial response for 4 months) is relevant towards taking a decision about whether the study and enrollment should continue or not. Van Glabbekea [7] considers that a response of more than 40% in a treatment is relevant when assessing the efficacy of that treatment.

Concomitantly, the progression free survival of 4.7 months for the group of 18 patients with metastatic soft tissue sarcoma treated in second line with ifosfamide and hyperthermia is an encouraging result.

The efficacy of locoregional hyperthermia (electro-hyperthermia) induced by the EHY-2000 device was demonstrated in preclinical studies where the main effects of electro-hyperthermia were classified in thermal effects (changes on ion-gradient and membrane potential, increase glicolitic activity, glucose and lactate, decrease hypoxia in tumors, increase of oxygen-free radicals, induction of heat shock proteins) and non-thermal effects (for electromagnetic fields 1–30MHz) – direct electromagnetic coupling on cancer cells.

The combination of chemotherapy and hyperthermia was reported with a pathological response rate of 42% in neoadjuvant chemo-hyperthermia treatment of soft-tissue sarcoma [12] with a median OS of 31 months. Correlated with this trial, where the response rate is 44%, this result suggests that the combination of hyperthermia + chemotherapy with ifosfamid can be promising related with progression free survival. Low rate of side-effects demonstrates that the combination of hyperthermia and chemotherapy with ifosfamid is a safe treatment. The extension of the group of patients with soft-tissue sarcoma is mandatory for more concludent data.

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