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Effect of high-dose ifosfamide in advanced soft tissue sarcomas. A multicentre phase II study of the EORTC Soft Tissue and Bone Sarcoma Group

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Abstract

In this phase II study the effect of high-dose ifosfamide (HDI) given as a 3-day continuous infusion at a dose of 12 g/m^2 repeated every 4 weeks with adequate mesna protection and hydration was evaluated in patients with advanced soft tissue sarcomas. A total of 124 patients entered the trial of which 10 were ineligible. HDI was given both as first-line and second-line chemotherapy. Median age was 46 years (19–66 years). Median World Health Organization (WHO) performance status was 1 (0–1). Fifty two per cent of the patients were males. The predominant histology was leiomyosarcoma (33%). A maximum of six cycles was given. At the time of analysis 55 patients have died. The partial response (PR) rate was 16%. The median time to progression was 15 weeks. 8 of the 18 responding patients (44%) had synovial sarcomas, whereas only 5% of the patients having leiomyosarcomas responded. The grade 3+4 haematological toxicity encountered was neutrophils in 78% and platelets in 12%. The major grade 3+4 non-haematological toxicities encountered were febrile neutropenia in 39%, infection in 20%, and acute renal failure in 4%. In conclusion, it is possible to administer HDI on a multicentre basis, but the toxicity is substantial. HDI given as a continuous infusion at this dose cannot be recommended as the standard treatment of advanced soft tissue sarcomas, even in selected patients.

Keywords: Chemotherapy; High-dose; Ifosfamide; Soft tissue sarcoma

1. Introduction

Soft tissue sarcomas are rare tumours accounting for approximately 1% of all malignancies. There are multiple histological subtypes, but these are usually grouped under the heading of a soft tissue sarcoma for the purpose of treatment. Local surgery and adjuvant radiotherapy is usually the first line of management [1–3], whereas the role of adjuvant chemotherapy has not yet been defined [4–6]. However, despite an optimal primary therapy this treatment will in many patients not prevent the occurrence of distant metastases. Conse-

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quently, chemotherapy has been extensively studied in soft tissue sarcomas. Unfortunately, their responsiveness to chemotherapy has been disappointingly low [4].

Doxorubicin appears to be the most active drug in the treatment of soft tissue sarcomas. During the last decade more than a thousand patients have been treated with the drug in connection with several reported studies. The cumulative response rate in non-pretreated patients was approximately 25% [4, 7]. Activity has also been noted in pretreated patients in an EORTC trial [8]. Doxorubicin treatment is limited because of cumulative cardiotoxicity, but unfortunately none of the tested anthracycline analogues has shown superiority or comparability with doxorubicin in terms of therapeutic activity with less toxicity [7].

A second active drug in the treatment of soft tissue sarcomas is ifosfamide. The initial non-randomised studies had shown response rates of 38–67% [4]. The European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) performed a randomised phase II trial comparing cyclophosphamide with ifosfamide. In this trial, the activity of ifosfamide was confirmed with a 25% response rate in non-pretreated patients [9]. Ifosfamide given at standard dose (SDI) has also demonstrated activity as second-line chemotherapy, although the activity was definitely lower than that observed in the front-line treatment. The use of mesna has allowed new investigational studies on dose intensity and novel schedules with ifosfamide. There is increasing evidence of a strong dose–response relationship for doxorubicin in advanced soft tissue sarcomas, and several studies have also suggested the likelihood of a comparable dose–response effect of ifosfamide [4, 10]. However, at present the optimal dose and scheduling of ifosfamide administration with respect to tumour effect and quality of life have not been settled.

A number of recent small studies [10–13] have investigated the effect of high-dose ifosfamide (HDI). In these studies HDI resulted in response rates higher than those obtained with SDI even in patients pretreated with standard chemotherapy, and interestingly even in many of them after prior ifosfamide at standard dose. Thus, the present data suggest a dose–response relationship at doses between 5 and 12 g/m^2 of ifosfamide. However, there is no firm evidence for a dose–response relationship at doses between 12 and 18 g/m^2 [11]. Thus, the current data on HDI do not justify the use of ifosfamide at doses above 12 g/m^2. HDI has been associated with substantial toxicity compared with SDI [10–13]. However, in most studies HDI appeared feasible and manageable [10].

The present data on HDI are interesting. However, these data all come from small studies, mostly single institutional, with the potential of a high risk of selection bias. Therefore, more data on its antitumour effect as well as toxicity in patients with advanced soft tissue sarcomas are definitely needed, and especially the feasibility of this regimen when used on a multicentre basis. In this EORTC phase II study the effect of ifosfamide given as a 3-day continuous infusion at a dose of 12 g/m^2 every 4 weeks was investigated.

2. Patients and methods

2.1. Study design and eligibility criteria

This study was an open non-randomised multicentre phase II trial. The principal objective of the trial was to assess the therapeutic activity of HDI in patients with advanced soft tissue sarcomas. Ifosfamide could be given both as first- and second-line chemotherapy and the patients were stratified accordingly. The endpoints were objective response, duration of response as well as acute and chronic toxicity. Patients fulfilling the inclusion criteria were registered at the EORTC Data Centre prior to the start of treatment and after verification of eligibility criteria and selection of target lesions.

The study was conducted in patients with histologically proven soft tissue sarcomas, who either had relapsed locally or developed metastases after primary surgery and/or radiotherapy, or who initially presented with advanced inoperable disease. Patients who had received more than one line of previous combination chemotherapy or two single-agent regimens were ineligible. Previous chemotherapy had to be discontinued for more than 4 weeks. Other eligibility criteria included: age between 18 and 65 years, performance status 0 or 1 on the World Health Organization (WHO) scale, no other severe medical illness including psychosis and previous history of cardiovascular disease, no prior malignant tumour (except for adequately treated carcinoma *in situ* of the cervix and/or carcinoma of the skin), no central nervous system (CNS) metastases, no prior nephrectomy, creatinine clearance $\geqslant 70$ ml/min, bilirubin $\leqslant 30$ μmol/l, albumin $\geqslant 25$ g/l, white blood cell (WBC) $\geqslant 4\times10^9$/l, platelets $\geqslant 100\times10^9$/l), and the presence of measurable lesions not previously irradiated with evidence of progression within 6 weeks prior to treatment. Specific minimum criteria for measurability were >2 cm for lung metastases and >2.5 cm for others. Patients with mesothelioma, chondrosarcoma, neuroblastoma, osteosarcoma, Ewing's sarcoma and embryonal rhabdomyosarcoma were excluded. Patients should be able to attend regular follow-up visits. Informed consent was obtained from all patients according to local and/or national rules.

2.2. Treatment schedule

The patients were given ifosfamide and mesna 12 g/m^2 as a 3-day continuous infusion followed by a further 4 g/m^2 12-h mesna infusion. Treatment cycles were repeated every 4 weeks. Sufficient diuresis was established before treatment using 1 l dextrose saline/2 h and 500 ml 20% mannitol/30 min. To prevent severe acidosis the patients received 150–180 mmol intravenous sodium bicarbonate daily during the 3-day ifosfamide infusion and the day after.

Treatment was delayed for 1 week if absolute neutrophil count was $<2\times10^9$/l and/or platelets $<100\times10^9$/l. Patients delayed for 3 weeks without haematological recovery were taken off the study. The total ifosfamide dose was reduced by 20% for subsequent cycles in cases of intertreatment periods with sepsis requiring hospitalisation and antibiotics. Patients were excluded from further study treatment if serum creatinine level exceeded 2.5×normal level between cycles and if creatinine clearance was <60 ml/min during the 4-week interval or at the time of the following cycle. In the event of grade 3 or 4 neurotoxicity patients were excluded from the study and in the event of grade <3 neurotoxicity the treatment was continued under careful observation. The use of methylene blue was allowed [14].

The total number of courses of ifosfamide was restricted to six. Ifosfamide was given for at least two courses, unless it was clearly not in the best interest of the patient, for example, in cases where there was a rapid progressive disease after one course or unacceptable toxicity. In cases of partial response or no change, treatment was continued to the maximum of six cycles unless disease progression or severe toxicity developed earlier. Whatever the disease status, the treatment was always discontinued in cases of patient refusal and excessive toxicity precluding further therapy.

2.3. Pretreatment and follow-up evaluations

Evaluation prior to treatment included history and physical examination, performance status, haematology (haemoglobin, WBC and differential, platelet counts), blood chemistry (urea, sodium, potassium, creatinine, calcium, glucose, bilirubin, alkaline phosphatase, aspantale aminotransferase (ASAT), alanine aminotransferase (ALAT), lactate dehydrogenase (LDU), albumin), urine analysis, creatinine clearance, tumour measurements, a plain chest radiograph, and a bone scan and/or radiography. Haematology and blood chemistry were performed weekly. During treatment physical examination, urine analysis and creatinine clearance were performed before every cycle. Chest X-ray and tumour measurements were carried out every second course. If the patient had not progressed, the disease was assessed every 8 weeks, following the same procedures as during treatment. After treatment completion the patient was followed every 12 weeks for survival.

2.4. Definition of response and toxicity

Patients were considered assessable for response if they had received at least two cycles of chemotherapy. Response was defined according to the WHO criteria. Progression-free and overall survival were computed from the start of treatment. The period of overall response was computed from the first day of treatment to the date of first observation of progressive disease. Patients progressing after one cycle were classified as treatment failures. Patients taken off study after one cycle due to toxicity were considered inevaluable for response but remained evaluable for toxicity. The toxicity was evaluated according to the NCI common toxicity criteria.

2.5. Statistical analysis

The Simon one-sample two-stage testing procedure was used in the trial (minimax design) with 10% as the largest response probability which, if true, would imply that the therapeutic activity did not warrant further investigation of the drug and 30% as the lowest response probability which, if true, would imply that the therapeutic activity did warrant further investigation of the drug. The total sample size for the trial was 25 patients; the trial should, however, be discontinued after 16 patients if $\leqslant1$ responses were observed. A second test was performed amongst the 25 patients, and only if there were more than four responses would the trial be stopped with the conclusion that the drug should be investigated further. In order to assess better the toxicity profile in a multicentre setting and allow analysis of histological subtypes the study was, however, continued beyond the planned sample size. Therefore, a total of 124 patients were included, of whom 25 patients had received prior chemotherapy (6 patients in an adjuvant setting).

If a new treatment was started before progression, the duration of response (or stabilisation) was 'censored' on the first day of the new treatment. All eligible patients were included in the analysis of side-effects unless they had not received any treatment. Exact 95% confidence intervals for proportions were calculated for response rates. Duration of response, progression-free and overall survival were estimated by use of the Kaplan–Meier method [15].

2.6. Quality control

A central pathology panel reviewed and graded histopathological material from patients entering the trial, according to the rules of the EORTC STBSG. Similarly all responding patients underwent an independent

Table 1
Patients characteristics

Characteristics	Number of patients (%)
Median age (range)	46 (19–66) years
Male	59 (52)
Female	55 (48)
Registered patients	124
Ineligible patients	10
Included patients	114
Performance status 0/1	50 (44)/64 (56)
Histology	
Leiomyosarcoma	38 (33)
Synovial sarcoma	22 (19)
Liposarcoma	13 (11)
Unclassified	9 (8)
Malignant fibrous histocytoma	8 (7)
Others	24 (21)
Site of the primary tumour	
Visceral	26 (23)
Uterus	11 (10)
Truncus	16 (14)
Retroperitoneum	11 (10)
Extremities	44 (39)
Other	6 (5)
Prior radiotherapy	
No	79 (69)
Yes	35 (31)
Prior chemotherapy	
No	89 (78)
Yes, adjuvant	6 (5)
Yes, advanced	19 (17)

Table 2
Dose intensity parameters

Ifosfamide parameters	Median (range)
Cycles	3 (1–8)
Total dose, g/m^2	34.9 (2.7–79)
Duration, days	84 (28–224)
Relative dose intensity, %	97 (22–205)

external response review according to the rules of EORTC STBSG. The quality control of the group has been described elsewhere [16].

3. Results

3.1. Patient characteristics

A total of 124 patients from 21 centres were included. 10 patients were considered ineligible for the trial for the following reasons: Patient treated before registration ($n=4$), inappropriate histology ($n=1$), no target lesion ($n=4$) and brain metastases ($n=1$). The analysis consequently was based on 114 patients; their demographic and clinical characteristics are summarised in Table 1. 89 (78%) patients had received no prior chemotherapy, 6 patients (5%) had received adjuvant chemotherapy and 19 patients (17%) had received chemotherapy for advanced disease. Prior ifosfamide was given to 13 patients (11%). One third of the patients had visceral and uterine tumours and the predominant histology was leiomyosarcoma (33%). In 59% of all patients the metastases were located in lungs, 26% in liver, and 37% in other locations. At the time of analysis 55 patients had died (48%).

3.2. Treatment compliance

The patients received a median of three cycles, ranging from 1 to 8 cycles. The dose intensity computed according to the Hryniuk method [17] was 97%. Dose intensity parameters are summarised in Table 2. The 205% relative dose intensity is due to 1 patient receiving 24 g/m^2 instead of 12 g/m^2 ifosfamide as a consequence of an accidental overdosing. The total treatment duration was computed as the difference between the first and last day of administration, plus 28 days, corresponding to the theoretical duration of the last cycle. The relative dose intensity of first-line (96%) and second-line chemotherapy (97%) did not differ from those of the whole group.

Table 3
Response to treatment

	No prior chemotherapy *n* (%)	Prior adjuvant chemotherapy *n* (%)	Prior chemotherapy advanced disease *n* (%)	All patients *n* (%)
CR	0 (0)	0 (0)	0 (0)	0 (0)
PR	15 (17)	0 (0)	3 (16)	18 (16)
NC	31 (35)	1 (17)	4 (21)	36 (32)
PD	35 (39)	5 (83)	8 (42)	48 (42)
Early deaths[a]	2 (2)	0 (0)	0 (0)	2 (2)
Not evaluable	6 (7)	0 (0)	4 (21)	10 (9)

[a] 1 patient due to PD, 1 patient due to cardiogenic shock.
CR, complete responders; PR, partial responders; NC, no change; PD, progressive disease.

Table 4
Haematological toxicity: number of patients (%) ($n=114$)

WHO grade	Grade 3 *n* (%)	Grade 4 *n* (%)
Leucopenia	27 (24)	70 (61)
Neutropenia	8 (7)	81 (71)
Thrombocytopenia	9 (8)	5 (4)
Haemoglobin	17 (5)	5 (4)

Table 5
Non-haematological toxicity: number of patients (%) ($n=114$)

WHO grade	Grade 3 *n* (%)	Grade 4 *n* (%)
Infection	18 (16)	4 (4)
Febrile neutropenia	45 (39)	0 (0)
Acute renal failure	2 (2)	2 (2)
Alopecia	19 (17)	0 (0)
Vomiting	12 (11)	1 (1)
Nausea	16 (14)	0 (0)
Anorexia	2 (2)	0 (0)
Constipation	6 (5)	0 (0)
Neurotoxicity	13 (11)	2 (2)
Lethargy	5 (4)	0 (0)

3.3. Response

The overall response data are shown in Table 3. All responses have been externally reviewed and all cases evaluated by the study co-ordinator. The 'progression' category includes early progressions as well as early deaths due to malignant disease. Of the 114 eligible patients 104 were evaluable for response. A total of 10 patients was unevaluable: 8 patients only received one cycle of treatment, 1 patient died of renal failure at week 11, and 1 patient refused further evaluation. 18 patients responded to therapy [response rate 16%, 95% confidence interval (CI) 9–23%]. In the patients receiving no prior chemotherapy the response rate was 17% (95% CI 10–26%) and in patients receiving prior chemotherapy for advanced disease it was 16% (95% CI 4–40%). Of the 3 patients responding to second-line HDI one patient had received prior ifosfamide. The median time to progression was 15 weeks (Fig. 1). The median duration of response estimated by the Kaplan–Meier method was 42 weeks.

8 of the 18 responding patients (44%) had synovial sarcomas. In the subgroup of 38 patients having leiomyosarcomas the overall response rate was 5% (2 patients). In patients with histological types other than leiomyosarcomas the overall response rate was 23% (2 malignant fibrous histocytomas, MFH, 2 angiosarcomas, 1 liposarcoma, 2 miscellaneous sarcomas). The most predominant tumour site among the responding patients was lung as 14 of the 18 responders (78%) had lung metastases. The primary tumour site was involved in 11, lymph nodes in 4, and liver in 2 of the responders.

3.4. Toxicity

The haematological toxicities expressed as the lowest value of haematological counts observed during the whole treatment are presented in Table 4, and thus represent the worst toxicity observed during therapy. The haematological toxicity was high with grade >4 toxicity in more than 60% of patients. The haematological toxicity after second-line chemotherapy did not differ from that of the other patients. As seen in Table 5 the non-haematological toxicities were less severe with only a few patients having grade 4 toxicities. Grade $3+4$ acute renal failures were seen in 4 patients. One patient died of renal failure, neurological toxicity and hepatitis after three cycles.

3.5. Survival

Progression-free and overall survival curves are shown in Figs 1 and 2. The 1-year progression-free estimate was 15% (standard error 5%). The median follow-up was 3 years (actuarial estimate), and 59 patients were

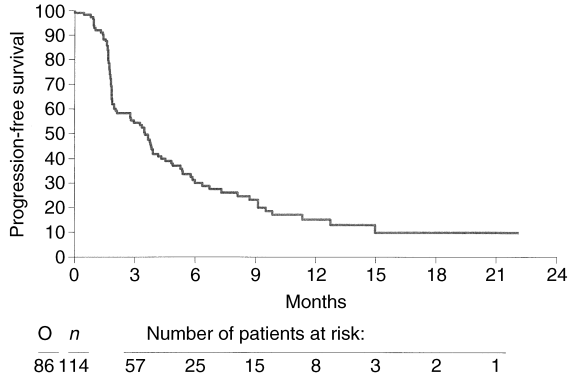

Fig. 1. Actuarial estimate of progression-free survival of patients with soft tissue sarcoma treated with high-dose ifosfamide. O, observed number.

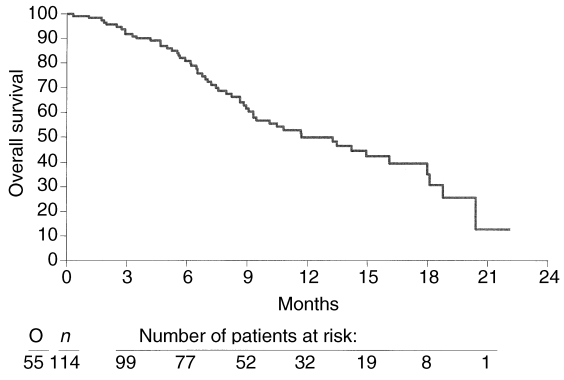

Fig. 2. Actuarial estimate of overall survival of patients with soft tissue sarcoma treated with high-dose ifosfamide. O, observed number.

still alive at the time of the data analysis. The cause of death was progression in 47 patients, toxicity in 1 patient, other in 5 patients, and unknown in 2 patients. The estimated median duration of survival was 55 weeks. The 1-year survival estimate was 50% (standard error 6%).

4. Discussion

In a review on ifosfamide in soft tissue sarcomas [18] it was concluded that ifosfamide is an active drug in soft tissue sarcomas but further data are needed to define the influence of ifosfamide dose and schedule. The use of mesna has allowed new investigational studies on dose intensity and novel schedules with ifosfamide, and a number of studies have suggested the likelihood of a dose–response effect of ifosfamide [4, 10, 18, 19]. The maximum tolerated dose was found to be 16–18 g/m^2 [20, 21]. HDI may be more active than standard dose regimens, but toxicity is substantial [10–13, 19]. In contrast, at doses between 12 and 18 g/m^2 there does not seem to be firm evidence for a dose–response relationship [11]. In the present study a response rate of 16% was obtained with HDI. The response rate after first-line chemotherapy is disappointing low and no better than the response rate with SDI. There may be a number of explanations for this low response rate. The independent external response review as performed in EORTC STBSG on all responding patients could in part explain the low response rate. In addition, the large proportion of visceral and uterine tumours (33%) as well as the large proportion of leiomyosarcomas (33%) may have reduced the response rate. As discussed by Le Cesne and colleagues [10] a number of studies may indicate that leiomyosarcomas are uniformly resistant to ifosfamide-based therapy. This suggestion was also supported by the present data as the response rate of leiomyosarcomas was only 5%. New strategies must therefore be developed for this chemoresistant histological subtype. In contrast, some studies have indicated that synovial sarcomas may be particularly chemosensitive to ifosfamide-based regimens [10, 11], although selection bias may to some extent also explain these results [22]. In future studies stratification for known prognostic factors should be considered in order to overcome the problems caused by the heterogeneity of recruited patients.

Another possible explanation for the low response rate of HDI could be the schedule of ifosfamide administration. A recent randomised study by EORTC STBSG showed a significantly higher response rate with 3 g/m^2 ifosfamide given as a 4-h daily infusion for 3 consecutive days compared with 5 g/m^2 ifosfamide given as a 24-h continuous infusion [23]. Although the total dose was different in the two treatment arms these data may indicate the importance of ifosfamide scheduling. Similarly, a number of phase II studies have indicated that the response rate may be higher with bolus/short-term infusion as compared with continuous infusion [18–20]. In a recent study [19] a response rate of 19% was obtained with ifosfamide 14 g/m^2 given as a continuous infusion, whereas the same total dose given as a bolus resulted in a response rate of 45%. However, these data may be misleading because of a low number of leiomyosarcomas in both groups and a high number of MFH in the bolus group. In contrast, a recent phase II study of HDI [24] found a response rate of 38% with ifosfamide 14 g/m^2 given as a continuous infusion, although leiomyosarcomas were the predominant subtype (38%). An increased response with continuous infusion was also noted in a study at the Dana-Farber Institute [20]. At the EORTC we are currently testing the importance of ifosfamide schedules in a randomised phase III study comparing 3 g/m^2 ifosfamide given as a 4-h daily infusion for 3 consecutive days, 9 g/m^2 ifosfamide given as a 72-h continuous infusion, and 75 mg/m^2 doxorubicin given as a bolus. In addition, the MD Anderson Cancer Center is further testing the bolus schedule. In the absence of these results, it appears that ifosfamide may be more active when administered as a short 2–4-h infusion than as a continuous infusion, although, in a recent study [25] the pharmacokinetics of ifosfamide continuous infusion did not differ from that of fractionated administration. Finally, we used a treatment interval of 4 weeks as opposed to other studies on HDI which used a 3-week interval [19, 22, 26, 27]. This difference in treatment interval could also in part explain the low response rate, although in the study by Le Cesne and colleagues [10] a response rate of 33% was obtained with the same schedule as in the present study. Thus, the available data indicate that the schedule of ifosfamide administration may be of importance, but they also point to the difficulties in drawing any definite conclusions at present.

The toxicity profile of the present study was comparable with that of other studies on HDI, that is, toxicity was substantial but manageable [10–13, 19, 22, 27]. We used no haematopoietic growth factors and the high frequency of grade 4 neutropenia was expected. There was also a high frequency of non-haematological toxicity, particularly febrile neutropenia and infection (Table 5). There was a small but a definite increased incidence of acute renal failure. Prevention of renal acidosis may potentially protect patients from acute ifosfamide renal toxicity [10]. Thus, the relatively low incidence of significant renal toxicity in the present study was probably a result of the vigorous hydration and supplementation of bicarbonate to prevent severe metabolic acidosis. Severe reversible cardiac dysfunction secondary to HDI has been described in the literature [28]. However, in the present study only 1 patient

developed grade 3+4 cardiotoxicity (tachycardia). Similarly, severe neurotoxicity was also rare (2%) as opposed to the high incidence described in some studies [10].

In conclusion, it is possible to administer HDI at a total dose of 12 g/m^2 on a multicentre basis. However, although the effect of HDI was not directly compared with that of SDI, its activity does not seem to be higher than that obtained with SDI, and although manageable, the toxicity is substantial. At present, HDI given as a continuous infusion cannot be recommended as the standard treatment of advanced soft tissue sarcomas even in selected patients, and further studies examining the importance of dose and schedule of ifosfamide are needed.

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