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European Journal of Cancer 39 (2003) 488–494

European Journal of Cancer

www.ejconline.com

Scandinavian Sarcoma Group Osteosarcoma Study SSG VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders

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Received 10 June 2002; received in revised form 7 October 2002; accepted 14 November 2002

Abstract

From 1990 to 1997, 113 eligible patients with classical osteosarcoma received neo-adjuvant chemotherapy consisting of high-dose methotrexate, cisplatin and doxorubicin. Good histological responders continued to receive the same therapy postoperatively, while poor responders received salvage therapy with an etoposide/ifosfamide combination. With a median follow-up of 83 months, the projected metastasis-free and overall survival rates at 5 years are 63 and 74%, respectively. Independent favourable prognostic factors for outcome were tumour volume <190 ml, 24-h serum methotrexate >4.5 μM and female gender. The etoposide/ifosfamide replacement combination did not improve outcome in the poor histological responders. In conclusion, this intensive multi-agent chemotherapy results in $>70\%$ of patients with classical osteosarcoma surviving for 5 years. The data obtained from this non-randomised study do not support discontinuation and exchange of all drugs used preoperatively in histological poor responders. As observed in previous Scandinavian osteosarcoma studies, female gender appears to be a strong predictor of a favourable outcome.

Keywords: Osteosarcoma; Clinical protocols; Chemotherapy; Neo-adjuvant therapy; Limb salvage; Prognosis; Scandinavia; Sex

1. Introduction

Adjuvant chemotherapy has significantly improved the outcome of patients with high-grade osteosarcoma [1–3]. Although never proven in controlled trials, neo-adjuvant therapy is generally agreed upon as the optimal treatment schedule. In addition to facilitating limb salvage surgery, it offers an opportunity to tailor postoperative chemotherapy after evaluation of histological response in the surgical specimen [4]. With this strategy, long-time overall survival rates of 70% are reported, and more than 80% of the patients can currently be expected to be operated upon with limb salvage surgery in major centres [5–9].

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PII: S0959-8049(02)00747-5

Histological response as assessed by chemotherapy-induced tumour necrosis is regarded as a strong prognostic factor in osteosarcoma [4,7,10,11]. Consequently, a more intensive preoperative chemotherapy with more patients obtaining a favourable histological response has been associated with an improved outcome [6,9,12,13]. In the preceding Scandinavian SSG II study (1983–1990), single high-dose methotrexate was given preoperatively with only 17% of the patients achieving a good histological response [5]. In an attempt to increase the number of good responders, the subsequent SSG VIII study utilised an intensified regimen with high-dose methotrexate, cisplatin and doxorubicin given preoperatively to all patients.

The effect of salvage therapy to improve outcome for poor histological responders is not well documented. Ifosfamide has been viewed as an attractive candidate due to its reported efficacy in relapsed patients [14,15]. Etoposide has less single-agent activity than ifosfamide, but has demonstrated synergy with ifosfamide in the treatment of sarcomas [16]. In addition, adding ifosfamide and etoposide to salvage therapy for poor responders appeared successful in the Rizzoli IOR-II study [6]. Based upon these data, poor histological responders in the current trial were treated by an ifosfamide/etoposide combination that replaced the three drugs given up-front.

2. Patients and methods

2.1. Patients

From May 1990 to December 1997, 132 patients with high-grade extremity osteosarcoma from 14 centres in Sweden, Norway and Finland, were entered into the SSG VIII study. Further eligibility criteria were age <40 years and no evident metastases as assessed by a mandatory chest computed tomography (CT) and whole body bone scan. 19 patients were excluded due to metastatic disease ($n=12$), non-extremity tumour ($n=3$), age >40 years ($n=1$), revised diagnosis of Ewing's sarcoma ($n=1$) or malignant fibrous histocytoma ($n=1$) and definitive intralesional surgery before referral ($n=1$), leaving 113 eligible patients. Patient characteristics are summarised in Table 1. The diagnosis of osteosarcoma was confirmed by open biopsy in all cases. One reference pathologist from each participating country reviewed all of the slides and agreed upon the diagnosis, subtype and malignancy grade. Plain X-ray, technetium 99-MDP bone scan, CT scan and for most patients magnetic resonance imaging (MRI) of the entire bone involved, was used to assess the primary tumour. The tumour volume at diagnosis was reviewed by an expert panel of radiologists. Measurements were based upon MRI scans when available or otherwise by CT scan. Either the cylindrical formula ($V=\pi abc$) or the elliptic formula ($V=4/3\pi abc$) were chosen; usually the cylindrical formula was the model of choice [17].

Table 1
Patient characteristics

	Number (all)	5-year metastasis-free survival (%)	P value (logrank) in univariate analysis
Gender			
Female	44 (113)	81	0.001
Male	69	52	
Age (years)			
<15 years	34 (113)	73	0.11
$\geqslant 15$ years	79	59	
Country			
Sweden	68 (113)	67	0.31
Norway	28	64	
Finland	17	47	
Site			
Humerus	15 (113)	59	0.61
Femur	60	63	
Tibia	31	61	
Others	7	86	
Histology			
Osteoblastic	60 (74)	62	0.76
Chondroblastic	4	64	
Fibroblastic	2		
Telangiectatic	0		
Others	8		
Tumour volume (ml)			
<190	49 (98)	75	0.01
>190	49	51	
LDH			
Normal	68 (105)	64	0.88
elevated	37	64	
ALP			
Normal	17 (104)	76	0.16
elevated	87	61	

LD, lactate dehydrogenase; ALP, alkaline phosphatase.

2.2. Chemotherapy

The chemotherapy regimen is outlined in Fig. 1. All patients were intended to receive two cycles of paired high-dose methotrexate (HD-MTX) together with a cisplatin/doxorubicin (CDP/ADM) combination preoperatively. Methotrexate was given as a 4-h infusion followed by leucovorin rescue starting 24 h after the start of HD-MTX. Up to February 1993, the methotrexate dose for patients aged >12 years was 8 g/m^2 and for younger patients 12 g/m^2. As a result of a lack of age-related differences in serum methotrexate levels in the preceding SSG II study, all subsequent patients received methotrexate at 12 g/m^2. Cisplatin (90 mg/m^2) was given intravenously (i.v.) as a 4-h infusion. Doxorubicin was given as a daily 4-h infusion at a dose of 25

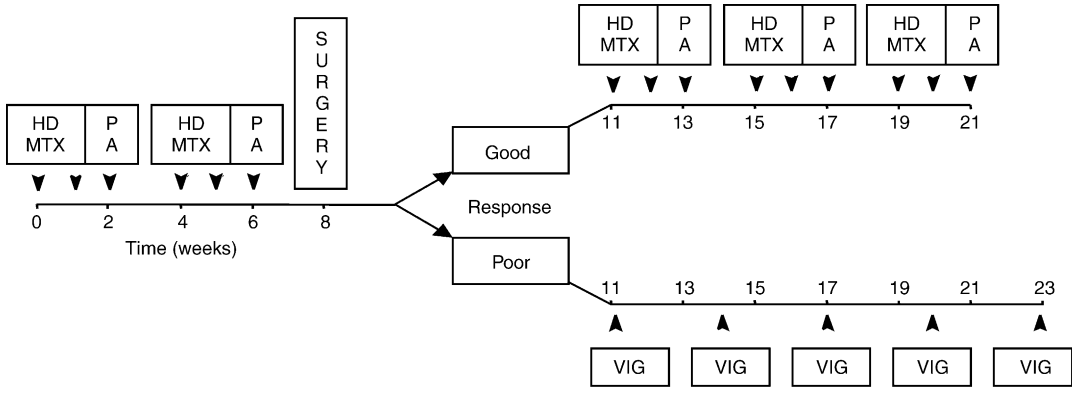

Fig. 1. Treatment schedule. HD-MTX = methotrexate 12 g/m^2, PA = cisplatin 90 mg/m^2, doxorubicin 75 mg/m^2. VIG = etoposide 600 mg/m^2, ifosfamide 4.5 g/m^2.

mg/m^2 for 3 consecutive days. Good responders were given three further cycles of methotrexate, cisplatin and doxorubicin postoperatively. The salvage regimen for poor responders consisted of 2-h infusions of 1.5 g/m^2 ifosfamide for 3 consecutive days in combination with a continuous 72-h infusion of 600 mg/m^2 etoposide (VIG regimen). Growth factor support with filgrastim was given after each VIG course and after CDP/ADM courses if a previous episode of febrile neutropenia had occurred. Good histological response was initially defined as Huvos grade II-IV. Based upon analyses of the SSG II study that revealed no difference in the outcome between grade I and II responders the current protocol was amended from February 1993, with grade II responders being treated as poor responders. Thus, due to the change of criteria for histological response, patients with Huvos grade II response were either given unchanged therapy or the VIG regimen. Relapse therapy was not included in protocol and left to the discretion of the responsible physician.

2.3. Pathological evaluation

Surgical margins were determined by the surgeon and the pathologist according to the classification of Enneking and colleagues [19]. The histological response to the preoperative chemotherapy was evaluated according to Huvos [20]. The initial pathological evaluation at each institution determined the postoperative chemotherapy. When possible (96%, $n = 108$), sections were reviewed for histological response by the three SSG reference bone tumour pathologists and this final evaluation was used in the prognostic factor analyses.

2.4. Response criteria and statistical analyses

Projected metastasis-free survival was calculated from the date of diagnosis until the date of distant metastasis or last follow-up. Event-free survival was calculated from the date of diagnosis until the date of distant metastasis, local recurrence, treatment-related death or last follow-up. Sarcoma-related survival was calculated from the date of diagnosis until death from osteosarcoma, treatment-related causes or last follow-up. For statistical analyses the Statistical Package SPSS for Windows (Release 10.1, SPSS Inc., Chicago, IL, USA) was used. The Kaplan–Meier method was used for the survival analysis and the curves were compared by the log-rank test. Missing values were not replaced by a default setting. A missing variable led to exclusion of the case in the analysis concerned. Continuous variables were categorised as below or above the median with the exception of age and alkaline phosphatase (ALP). Age groups were younger than 15 years or 15 years and older, and ALP was classified as normal or elevated after adjustment for age and gender according to Bacci [18]. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Compliance and toxicity

2 study patients were in need of prompt surgical treatment and did not receive neo-adjuvant chemotherapy: one because of an acute bacterial infection following tumour biopsy, the other due to pathological fracture after registration. The median delay from the start of chemotherapy to surgery was 20 days and the total treatment duration were 178 days in poor responders and 195 days in good responders. This represents a median delay of 66 days for good responders and 37 days for poor responders. 30% of the CDP/ADM courses and 8% of the VIG courses were followed by grade IV haematological toxicity. For 13 patients, chemotherapy was terminated early (less than 75% of intended dose was given) or modified in a major way because of toxicity. The individual drugs causing such major toxicity were methotrexate in 9 cases, cisplatin in 3 cases and unknown for 1 patient. We recorded three

treatment-related deaths. One patient (a good responder) developed acute myelogenous leukaemia within a year of diagnosis and died 16 months later. The second patient died of acute cardiac arrest aged 19 years, 26 months after the termination of chemotherapy. She had received 370 mg/m^2 of doxorubicin, and the diagnosis of anthracycline-induced cardiomyopathy was confirmed at autopsy. The third patient died postoperatively of acute respiratory distress syndrome after metastasectomy for pulmonary relapse. 7 patients who progressed radiologically and/or clinically during therapy were switched to an ifosfamide-based therapy, either the VIG regimen or high-dose ifosfamide (continuos infusion of 15 g/m^2 in 5 days). All these patients later developed distant metastases.

3.2. Surgery and local control

66 patients (58%) were treated with limb salvage surgery or rotation-plasty. In the period of 1990–1993, 42% were operated upon with a limb salvage approach compared with 77% in the period of 1994–1997. Information on the surgical margins was available for 106 patients. 87% of the patients operated upon with a limb salvage technique and 96% of the amputated patients obtained wide or radical margins according to Enneking [19]. 8 patients (7%) developed local recurrence at an average time of 20 months (range 5–36 months) from diagnosis. 6 of these patients were operated upon with wide margins. Of the 8 patients with local recurrence, only 1 did not develop distant metastases and is alive and in second complete remission, 42 months after local recurrence. 5-year projected risk of local recurrence is 7.5% (95% Confidence Interval (CI), 5–10%).

3.3. Histological response and postoperative chemotherapy

At the primary assessment, 63% of the patients were classified as having a good response. After review by the reference pathologist, the response grading was altered in 33 out of 108 tumours (31%). In most cases, the revised response remained within the same major response category (good/poor), and following revision 58% remained good histological responders. In the group of 41 patients with a revised grade II histological response (true histological grade II responders), 16 patients received an unchanged therapy (HD-MTX and CDP/ADM) postoperatively, 20 patients the ifosfamide/etoposide combination and 5 patients received a major modification of up-front chemotherapy other than the ifosfamide/etoposide combination due to toxicity or progression.

3.3.1. Survival and postrelapse outcome

With a median follow-up of 83 months for survivors (range 42–124 months), 80 patients are currently alive and 78 patients are in complete remission. The projected sarcoma-related survival at 5 years is 74% (70–78%) (Fig. 2). 68 patients (60%) are alive in first complete remission. Of the 43 (38%) patients who have relapsed, 12 are in second complete remission. The projected metastasis-free survival at 5 years is 63% (58.5–67.5%). The average time to distant metastasis was 18 months (range 1–62 months). The projected event-free survival at 5 years is 61% (56.5–65.5%), including one local recurrence and two treatment-related deaths in addition to the metastatic relapses. In a separate survival analysis of true histological grade II responders, there was a non-significant difference in metastasis-free survival in favour of the unchanged therapy compared with the salvage therapy (Fig. 3). The 5 patients that received a major modification of up-front chemotherapy other than the etoposide/ifosfamide combination were excluded from this analysis. Of these 5 patients, 3 are alive in first complete remission and 2 are dead of their disease.

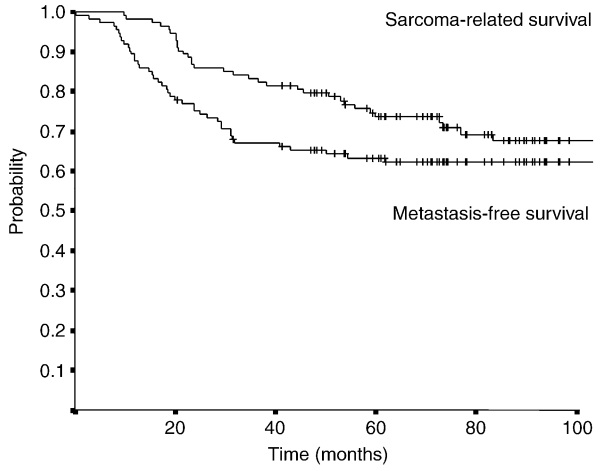

Fig. 2. Sarcoma-related and metastasis-free survival ($n = 113$).

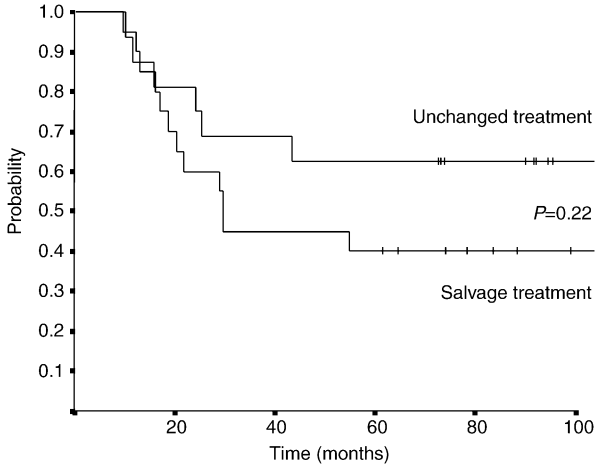

Fig. 3. True Huvos grade II responders—metastasis-free survival by postoperative chemotherapy. Unchanged treatment ($n = 16$): high-dose methotrexate, cisplatin and doxorubicin; salvage treatment ($n = 20$): etoposide and ifosfamide.

Of the 42 patients who developed distant metastases, 35 (83%) had lung metastases, 3 had skeletal metastases only and 4 had metastases at other locations. Relapse treatment was not defined by protocol and varied between centres; 73% received second-line chemotherapy and 76% underwent surgery. The overall survival at 5 years from relapse was 21%. For patients that were rendered macroscopically disease-free by metastasectomy, the corresponding survival rate was 38%.

3.4. Prognostic factor analyses

The following factors were taken into the univariate analyses of metastasis-free survival: age, gender, tumour volume, lactate dehydrogenase (LDH), ALP, site, type of surgery, serum-methotrexate (peak, 24 and 48 h values), histological response and type of postoperative chemotherapy (Tables 1 and 2). Independent favourable prognostic factors for outcome were female sex, tumour volume below median (190 ml, range 15–936 ml), and 24-h serum methotrexate serum-level above median (4.5 μM, range 1.0–7842 μM). Histological response to preoperative chemotherapy was not an independent prognostic factor in this analysis (Table 3).

Table 2
Treatment characteristics

	Number (all)	5-year metastasis-free survival (%)	*P* value (logrank) in univariate analysis
Surgery			
Amputation	46 (112)	56	0.28
Resection	66	68	
Margins			
Adequate	96 (106)	63	0.53
Inadequate	10	50	
Methotrexate serum peak (μmol/l)			
<1000	28 (86)	64	0.9
>1000	58	58	
Methotrexate serum level at 24 h (μM)			
<4.5	53 (106)	58	0.26
>4.5	53	67	
Response grade			
I	6 (111)	50	0.03
II	41	51	Good versus poor
III	49	69	
IV	15	87	
VIG postoperatively			
No	77 (113)	68	0.14
Yes	36	53	
Treatment duration			
<Median	45 (90)	55	0.31
>Median	45	64	

Table 3
Cox regression analysis of prognostic factors

Factor	Grouping	*n*	*P* value	HR	95% CI
Gender	Male	68	0.002	3.7	1.59–8.66
Age (years)	>15	79	NS		
Tumour volume (ml)	>190	50	0.017	2.4	1.18–5.05
Histological response	Good	64	NS		
Mean methotrexate at 24 h (μM)	>4500	53	0.017	0.4	0.21–0.88
VIG postoperative	Yes	36	NS		

HR, hazard ratio; CI, Confidence Interval; NS, non-significant.

4. Discussion

The survival data in the present study are comparable to the best published results, which are all obtained with combinations of the three or four most effective chemotherapeutic agents [6,9,21]. The SSG VIII survival data show a 9% increase in 5-year sarcoma-related survival compared with the SSG II study utilising the T-10 protocol [5].

During the study period, there was a considerable development towards more limb saving surgery with 3 out of 4 patients being operated upon with limb preservation from 1994 to 1997. This major achievement was obtained without an increase in the local recurrence rate compared with the SSG II study (7% versus 5%). The study confirms the association between local recurrence and metastatic disease as only 1 out of 8 relapsed patients is still alive.

Histological response is generally regarded as an important prognostic factor in osteosarcoma. The rate of good responders increased from 17% in our previous study [5] to 58% in the present study. This improvement in histological response did not translate into a comparative improvement in survival. This finding is in agreement with recent results from the Rizzoli Institute [22]. Thus, the fraction of patients achieving a favourable response cannot be regarded as a surrogate endpoint for survival. In a recent large study by the COSS group, histological response emerged as a key prognostic factor [11]. The survival difference between poor and good responders was comparable to that in our study (22–25%), and the fact that the histological response did not reach independent significance in the present study may merely reflect the relatively limited number of patients included.

Our results show that in poor responders replacement salvage chemotherapy with ifosfamide and etoposide failed to improve outcome. One reason may be that our ifosfamide dose was too low. Recently, Patel and colleagues documented a dose–response relationship for ifosfamide in osteosarcoma and recommended a dose of >10 g/m^2 [23]. In addition, the choice of etoposide may be questioned, as doxorubicin and etoposide have similar

mechanisms of action and share mechanisms of drug resistance [24]. Furthermore, the basis for withdrawal of the preoperative regimen in poor responders appears questionable in retrospect. The sub-group analysis of the true grade II histological responders indicates that a poor histological response does not equal chemoresistance. In the Rizzoli IOR-II study that showed a similar prognosis for good and poor histological responders, etoposide and ifosfamide were added to the up-front regimen in poor responders [6]. Our data support this strategy.

Modern osteosarcoma chemotherapy is very intense and several authors report reductions in dose-intensity which in turn may affect outcome [3,13,25]. We report a considerable toxicity-related prolongation in treatment. The use of growth factor support to overcome neutropenia may explain the shorter delay for the VIG regimen. However, this was not translated into a survival benefit. Methotrexate gives an opportunity to resume treatment despite incomplete bone marrow recovery and may have improved the overall treatment intensity and the results for patients treated with HD-MTX in the postoperative phase.

As other studies have shown, tumour volume was an important tumour-related factor predicting relapse [11,22,26]. Tumour volume is a candidate factor for stratification for therapy in a risk-adapted approach to osteosarcoma treatment. However, 2 out of 13 patients with a very small tumour volume (below 70 ml) died of their disease, demonstrating that small tumours can also be aggressive. As in SSG II, the methotrexate serum level at 24 h retained an independent prognostic value in the present study, whereas peak levels were not significant. Our study, with most patients receiving a dose of 12 g/m^2 confirms the importance of an adequate serum methotrexate level for outcome [27], and that doses of 12 g/m^2 methotrexate in patients up to 40 years of age is feasible. We would argue for tailoring of the methotrexate doses according to serum levels to ensure an adequate serum-level is obtained in most patients. Gender, in agreement with results from the SSG II study, is a prognostic factor for outcome, with a better prognosis for girls and women [28]. This gender difference is not observed in historical controls treated at the Norwegian Radium Hospital with surgery only or patients given sub-optimal chemotherapy [29,30]. We suggest that this may reflect some unknown gender-dependent genetic factor that is important for treatment efficacy.

In conclusion, the current study shows that intensive combination chemotherapy combined with centralised surgery resulted in a 5-year survival rate of 74%. Most patients were operated upon using a limb salvage approach. Prognostic factor analyses revealed female gender, small tumour volume and high serum-methotrexate as favourable factors for outcome. In this non-randomised study, adjusting chemotherapy by a complete change of the drugs used in the poor responders failed to improve outcome. Our findings, supported by previous results [6], indicate that if a salvage strategy is chosen, it should be given in addition to, and not as a replacement for, first-line therapy.

Acknowledgements

The authors thank Evy Nilsson at the study secretariat for her active participation in the project. This work was supported by the Swedish Cancer Foundation, the Nordic Cancer Union and the Norwegian Foundation for Health and Rehabilitation.

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