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SFOP OS94: A randomised trial comparing preoperative high-dose methotrexate plus doxorubicin to high-dose methotrexate plus etoposide and ifosfamide in osteosarcoma patients ☆

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ABSTRACT

The SFOP-OS94 randomised multi-centre trial was designed to determine whether preoperative chemotherapy regimen combining high-dose methotrexate courses and etoposide-ifosfamide could improve the proportion of good histologic response (⩽5% viable cells) compared to a regimen based on high-dose methotrexate and doxorubicin, in children/adolescents with localised high-grade limb osteosarcoma. Postoperative chemotherapy was adapted to the histologic response.

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Overall, 234 patients were randomised between 1994 and 2001. There were 56% good responders in the etoposide-ifosfamide arm versus 39% in the doxorubicin arm (p-value = 0.009). With a median follow-up of 77 months, the 5-year event-free survival of the entire population was 62%, slightly greater in the etoposide-ifosfamide arm than in the doxorubicin arm, but the difference was not significant (Hazard Ratio: HR = 0.71, 95%CI: 0.5–1.06, p-value = 0.09). Five-year overall survival of the entire population was 76%, similar in both arms (HR = 0.95, 95%CI: 0.6–1.6, p-value = 0.85). Toxicity was manageable with different acute toxicity profiles between treatment arms. No acute toxicity related death was reported. About 43% of the patients in the etoposide-ifosfamide arm were event-free at 3 years without having received any doxorubicin or cisplatin, thus avoiding the risk of long-term cardio- and ototoxicity.

Preliminary results of the study have been presented at the SIOP meeting, Brisbane, 2001 and at the ASCO meeting, Orlando, 2002.

Audited by the French Competent Authority: AFSSAPS (Agence Française de Sécurité SAnitaire des Produits de Santé).

Registered in the Clinical Trials.gov registry. Trial number: NCT00180908.

1. Introduction

Osteosarcomas are highly malignant tumours arising mainly in long bones. Neoadjuvant or adjuvant polychemotherapy has led to prognostic improvement compared to surgery alone, with relapse-free survival of 50% to 80%.[1–5] Phase-2 trials have demonstrated the efficacy of high-dose methotrexate (HD-MTX),[6] doxorubicin,[7] cisplatin[8] and more recently ifosfamide.[9,10] Most of the current strategies deliver these three or four drugs preoperatively.

In order to limit acute and long term toxicity of multi-drugs combination, we preferred another strategy combining, preoperatively, seven HD-MTX courses and two doxorubicin courses,[11] the other drugs being reserved for salvage treatment of patients having a poor response to the initial treatment.

Between 1992 and 1995, we conducted a phase-2 study combining etoposide (300 mg/m^2) and ifosfamide (12 g/m^2) in 27 heavily pre-treated osteosarcoma patients.[12] Overall response rate was 48%. Other authors have reported a high response rate with this drug combination.[13,14]

The best combination of preoperative chemotherapy remains controversial and this prompted us to conduct a randomised trial in children and adolescents with osteosarcoma, testing the hypothesis that HD-MTX plus etoposide and ifosfamide might improve the number of good histologic responses compared to HD-MTX plus doxorubicin.

2. Patients and methods

2.1. Study design

A multi-centre randomised trial comparing efficacy and safety of two preoperative chemotherapy regimens, both based on HD-MTX courses given alternately either with doxorubicin (standard treatment) or with etoposide-ifosfamide (new treatment).

2.2. Eligibility criteria and pretreatment evaluation

Eligible patients were patients treated for a non metastatic limb osteosarcoma under 20 years of age. Other eligibility criteria were biopsy-proven high-grade osteosarcoma excluding juxtacortical sarcoma and microcellular anaplastic sarcoma, no previous treatment, no contraindication to chemotherapy and no previous malignancy. Written informed consent was obtained from the parents and from patients aged 18 or above. The local ethics committees approved the protocol.

The histological slides were centrally reviewed by one pathologist blinded to group assignment. In doubtful cases, initial imaging and biopsy specimens were reviewed by a panel of six radiology and bone pathology experts. The tumours were classified according to WHO criteria. Preliminary staging included plain radiography and MRI of the involved bone, bone scintigraphy, chest X-ray and CT-scan.

2.3. Randomisation

Eligible patients were randomised by fax to the doxorubicin or etoposide-ifosfamide arm. A centralised randomisation software was used, with permuted blocks of size four and stratification according to centre category in three strata: the largest centre, all other large centres, all small centres.

2.4. Treatment (Fig. 1)

2.4.1. Preoperative chemotherapy

The doxorubicin arm consisted of seven courses of HD-MTX (12 g/m^2) in 1.0 litre of 5% dextrose in water with 1 mEq/kg of sodium bicarbonate administered as a 4-h infusion. Oral rescue with leucovorin began 20 h after each methotrexate infusion at a dose of 15 mg up to a total of 11 doses given every 6 h. Hydration and alkalinisation were performed orally or intravenously (i.v.) to achieve urine output of 1.600 L/m^2 for the first 24 h and 2.000 L/m^2 for the next 48 h with urine pH in excess of 7.0. Serum methotrexate levels and renal function were monitored daily. HD-MTX was administered on weeks 1, 2, 3, 6, 7, 10 and 11. Doxorubicin (70 mg/m^2) was administered as a 6-h continuous i.v. infusion on weeks 4 and 8.

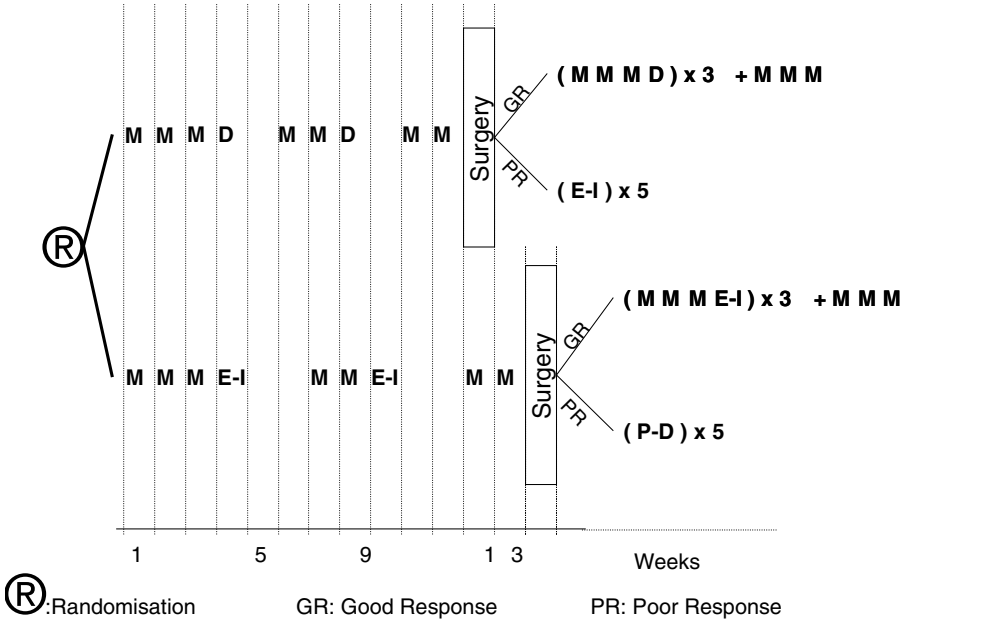

Fig. 1 – Treatment plan.

The etoposide-ifosfamide arm consisted of seven courses of HD-MTX given on weeks 1, 2, 3, 7, 8, 12 and 13. Etoposide (75 mg/m^2 i.v.) over 1 h in 250–500 mL saline serum and ifosfamide (3 g/m^2/day i.v.) over 3 h in 250–500 mL saline serum were given daily for 4 days during weeks 4 and 9. Mesna (3.6 g/m^2/day) was given as a continuous infusion for 4 days, with hydration up to 2.0 L/day.

2.4.2. *Surgery*

Surgical excision of the primary tumour was planned during week 12 in the doxorubicin arm and week 14 in the etoposide-ifosfamide arm.

2.4.3. *Postoperative chemotherapy*

Postoperative chemotherapy was adapted to the histologic response.

Doxorubicin arm: good responders received 12 courses of HD-MTX and three courses of doxorubicin and poor responders received five courses of etoposide-ifosfamide.

Etoposide-ifosfamide arm: good responders received 12 courses of HD-MTX and three courses of etoposide-ifosfamide and poor responders received five courses of cisplatin (120 mg/m^2) and doxorubicin (70 mg/m^2).

2.5. *Response assessment*

The surgical specimen was assessed by the local pathologist blinded to group assignment. The histologic analysis of the tumour map was performed according to Huvos method.[15] The mean percentage of residual viable cells was recorded. A good histologic response was defined as total or almost total necrosis ($\leqslant$5% of viable cells). All the histological reports and tumour maps were reviewed by the senior author to validate the conclusion, blinded to group assignment.

2.6. *Follow-up*

After completion of chemotherapy, chest X-rays were performed every 2 to 3 months for 3 years, every 4 months during the following 2 years and yearly thereafter. Bone scintigraphy was performed every 6 months during the first 3 years.

2.7. *Statistical considerations*

2.7.1. *End point – sample size*

The primary endpoint was a good histologic response after preoperative chemotherapy.

Secondary endpoints were event-free survival (EFS), overall survival (OS) and toxicity. OS rates were estimated, using the Kaplan–Meier method, from the date of randomisation to death or the date of the last follow-up visit for patients last seen alive. EFS rates were estimated, using the same method, from randomisation to the time of first failure (loco-regional or distant relapse, second malignancy or death) or to the last follow-up visit for patients in first complete remission. Suspected local progression of the primary tumour before surgery was not considered as an event. Median follow-up was estimated using the inverse Kaplan–Meier method.[16] Acute toxicity was assessed using the World Health Organisation (WHO) toxicity scale for children.

The trial was designed to demonstrate a 20% absolute improvement from 50% to 70% in the rate of good histologic responses. A total of 206 patients was required to reach a power of 80% with a Type-I error of 5% (two-sided test, Casagrande and Pike). The investigators decided to include 226 patients given the planned interim analysis.

2.7.2. *Planned analysis*

Analyses included all randomised patients, except those found not to have a malignant bone tumour at central histological review.

The efficacy analyses were stratified on centre category, using logistic regression for the analysis of the response rate considering a poor histological response as a failure, and using the Cox model for survival analyses.

Toxicity rates were compared using Chi-square tests.

Secondary analyses used logistic regression to study variations in treatment effects according to major baseline characteristics (age, tumour size) and to centres. All reported *p*-values are two-sided.

Data were entered and checked with the PIGAS software[17] and analysed with the SAS software® (version 8.2; SAS Software, Cary, NC).

One interim analysis was planned after inclusion and response assessment of 120 patients, using Pocock's plan.[18] Its result was seen only by the trial statistician.

3. Results

3.1. Accrual – study population

Between June 1994 and June 2001, 239 patients were included by 28 SFOP centres: 119 were allocated to the doxorubicin arm and 120 to the etoposide-ifosfamide arm. The histological review, performed centrally for 209 of the 239 randomised patients, led to the exclusion of five patients found not to have a malignant bone tumour. The study population therefore included 234 patients: 116 in the doxorubicin arm and 118 in the etoposide-ifosfamide arm (Fig. 2). Table 1 shows baseline patient characteristics.

Five patients with a malignant bone tumour other than high-grade osteosarcoma and six patients with initial metastases before randomisation were randomised despite not being eligible; they are included in the analyses according to the intention-to-treat principle.

The histologic response to chemotherapy, based on the surgical specimen, was assessed in the 234 patients.

Median follow-up was 77 months for the whole population. All patients were followed up for more than 3 years, and up to a maximum of 10 years.

3.2. Treatment

Chemotherapy was started at a median interval of 9 days after the biopsy (range: 1 to 55 days).

3.2.1. Preoperative chemotherapy protocol

Among the 116 patients allocated to the doxorubicin arm, 86 (74%) received at least the seven HD-MTX courses and the two doxorubicin courses required by the protocol, 15 of them received one or two additional courses of HD-MTX or doxorubicin. Fourteen patients (12%) received only six HD-MTX plus the two doxorubicin courses; these minor deviations were mainly due to the planned date of surgery. Sixteen patients (14%) received less than six courses of HD-MTX and/or less than two doxorubicin courses because of toxicity or suspicion of tumour progression; they are considered as a major deviation from preoperative chemotherapy protocol.

Among the 118 patients allocated to the etoposide-ifosfamide arm, 94 (80%) received at least the seven HD-MTX courses and the two etoposide-ifosfamide courses required by the protocol and 15 of them received one or two additional courses of HD-MTX. Twelve patients (10%) received only six HD-MTX plus the two etoposide-ifosfamide courses; these minor deviations were mainly due to the planned date of surgery. Twelve patients are considered as major deviation from preoperative chemotherapy protocol: 11 patients received less than six courses of HD-MTX or less than two courses of etoposide-ifosfamide because of toxicity or suspicion of tumour progression; an additional patient refused the allocated treatment and received the regimen administered in the doxorubicin arm.

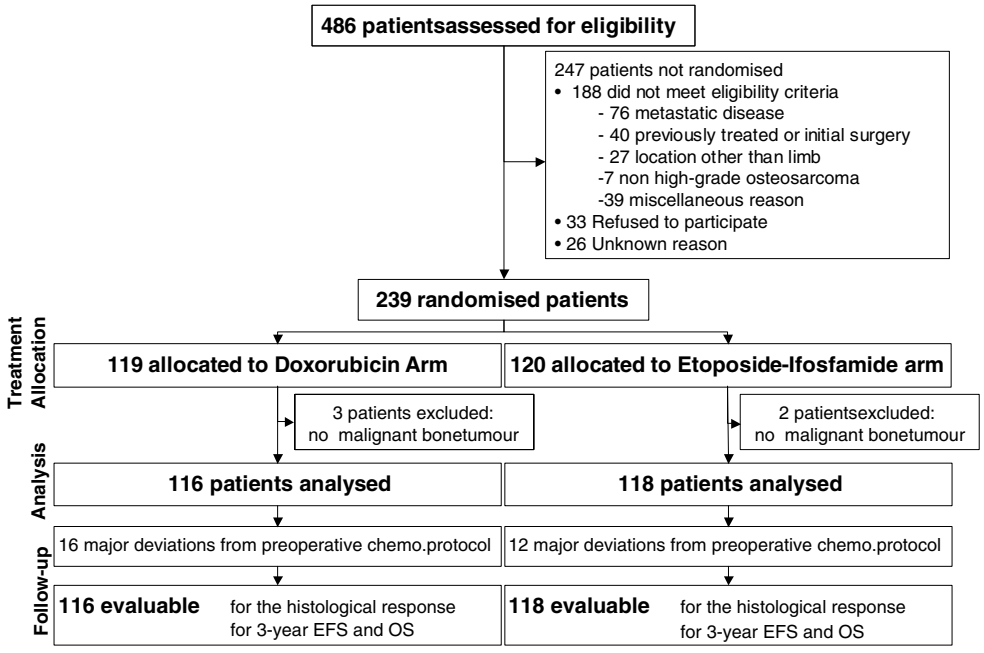

Fig. 2 – Trial profile.

Table 1 – Patient characteristics by treatment arm

Characteristics	Treatment arm		
	Doxorubicin (n = 116)	Etoposide-ifosfamide (n = 118)	Total (n = 234)
Age in years			
Median (range)	13.2 (3.1–19.5)	13.3 (5.5–19.3)	13.2 (3.1–19.5)
Sex			
Male	51%	61%	56%
Tumour location			
Lower limb, lower extremity femur	45%	47%	46%
Lower limb, upper extremity tibia	20%	23%	21%
Lower limb, other	21%	21%	21%
Upper limb	14%	9%	12%
Disease extension at diagnosis			
Metastatic disease	2%	3%	3%
Tumour size			
$\geqslant$10 cm	50%	44%	47%
Alkaline phosphatase			
$\geqslant 2 \times$ upper limit normal	23%	27%	25%
Histological subtype			
Common type	67%	61%	64%
Chondroblastic	11%	21%	16%
Fibroblastic	11%	10%	11%
Giant cells	4%	2%	3%
Telangiectatic	6%	0%	3%
Unclassified high-grade osteosarcoma	0%	2%	1%
Other[a]	1%	4%	2%

a Two juxta-cortical osteosarcomas: one per arm; two microcellular anaplastic osteosarcomas and one unclassified malignant bone tumour: all three in the etoposide-ifosfamide arm.

All patients were analysed according to the allocated treatment regardless of compliance.

3.2.2. *Surgery*

All patients underwent surgery 14.3 weeks (median) after the start of chemotherapy (inter-quartile range, 13 to 15 weeks, range 12 days to 27 weeks); this median time was 13.4 weeks in the doxorubicin arm and 15.0 weeks in the etoposide-ifosfamide arm.

Conservative surgery was performed in 221 patients (94%) and amputation in 13 patients (6%), nine in the doxorubicin arm and four in the etoposide-ifosfamide arm (p-value = 0.16).

3.2.3. *Postoperative chemotherapy protocol*

All but two patients received postoperative chemotherapy. To describe the postoperative chemotherapy regimen, we have excluded the six patients from the doxorubicin arm and the three from the etoposide-ifosfamide arm who received non-protocol courses preoperatively.

Among the 45 good responders after the doxorubicin arm regimen, 38 patients (84%) received three doxorubicin courses and nine HD-MTX courses or more. Among the 65 poor responders after the doxorubicin arm regimen, 61 patients (94%) received four courses of etoposide-ifosfamide or more.

Among the 66 good responders after the etoposide-ifosfamide arm regimen, 56 patients (85%) received three courses of etoposide-ifosfamide and nine HD-MTX courses or more. Among the 49 poor responders after the etoposide-ifosfamide arm regimen, 36 patients (73%) received four courses of cisplatin-doxorubicin or more.

3.2.4. *Toxicity*

3.2.4.1. Chemotherapy-induced acute toxicity. Information on acute toxicity was available for 98% of the 2027 preoperative protocol courses.

No patient died of chemotherapy-induced acute toxicity. During preoperative chemotherapy, more patients experienced at least one episode of haematological toxicity in the etoposide-ifosfamide arm than in the doxorubicin arm (80% versus 65%, p-value = 0.01). Severe neutropenia (neutrophil count $<500 \times 10^9$/l) was observed in 74% of the patients in the etoposide-ifosfamide arm versus 59% of the patients in the doxorubicin arm (p-value = 0.02) and was associated with fever in 38% versus 17% of cases respectively. Transfusions were given to 37% of the patients in the etoposide-ifosfamide arm versus 18% in the doxorubicin arm (red cell transfusion: 34% versus 17%, respectively; platelet transfusion: 14% versus 5%, respectively). On the contrary, more patients in the doxorubicin arm experienced at least one episode of non-haematological toxicity than in the etoposide-ifosfamide arm (79% versus 63%, p-value = 0.005), mainly hepatotoxicity (transaminases elevation $>10 \times$ ULN, 66% versus 42%, $p < 0.001$).

A transient reduction of left ventricular shortening fraction was reported in four patients of doxorubicin arm, without clinical signs. Two patients experienced neurotoxicity, one in each arm: one drowsiness during ifosfamide infusion

and one seizure related to HD-MTX. Six patients experienced glomerular impairment, two in the etoposide-ifosfamide arm and four in the doxorubicin arm; five were related to HD-MTX and one to antibiotics. A transient tubular dysfunction was reported in two patients of the etoposide-ifosfamide arm. Haematuria was observed in four patients of the etoposide-ifosfamide arm and in one patient of the doxorubicin arm; all but one occurred after ifosfamide course. In all these 19 patients, the treatment could be continued without modification.

3.2.4.2. *Second malignancies*. Six patients developed a second malignancy: a leiomyosarcoma of a limb 7.2 years after randomisation ($n = 1$), myelocytic acute leukaemia ($n = 4$) and myelodysplastic syndrome ($n = 1$), 1.4 to 2.7 years after randomisation. Four patients who developed a second malignancy had been treated in the doxorubicin arm (two good responders and two poor responders, including one who had received second-line treatment for an early postoperative relapse) and the two others in the etoposide-ifosfamide arm (both good responders). Four patients who developed haematological malignancy had received etoposide at a cumulative dose of 1500 mg/m^2 ($n = 3$) and 2400 mg/m^2 ($n = 1$); two of them had also received 140 mg/m^2 of doxorubicin; the fifth patient had not received etoposide but 350 mg/m^2 of doxorubicin.

3.3. Outcome

3.3.1. Histologic response to preoperative chemotherapy

Significantly more good responses were obtained in the etoposide-ifosfamide arm than in the doxorubicin arm: 56% versus 39% (p-value = 0.009). The results are similar when other cut-off values are considered: 64% versus 43% reported more than 90% necrosis (Fig. 3).

We did not observe any evidence of variation in this difference according to patient characteristics and the centre category; all interaction test p-values were above 0.45 (data not shown).

3.3.2. Event free and overall survival (Fig. 4)

The number of events (local or metastatic relapses, second tumours, deaths) was 54 in the doxorubicin arm and 41 in the etoposide-ifosfamide arm. The types of events are detailed in Table 2. The hazard ratio of events was 0.71 (95% CI: 0.5 to 1.06) in the etoposide-ifosfamide arm as compared to the doxorubicin arm. The difference was not statistically significant (p-value = 0.09). The 3-year EFS rates were 62% in the doxorubicin arm versus 69% in the etoposide-ifosfamide arm. No effect of randomised treatment on overall survival was observed (3-year OS, 84% and 83% respectively, hazard ratio = 0.95, 95% CI: 0.6 to 1.6, p-value = 0.85).

In the whole population, EFS was 66% at 3 years and 62% at 5 years and OS was 83% and 76%, respectively. As shown in Fig. 5, EFS and OS were significantly higher in good responders than in poor responders (3-year EFS 79% and 54%, 3-year OS 93% and 75% respectively). In the doxorubicin arm, 3-year EFS was 82% in good responders and 49% in poor responders. In the etoposide-ifosfamide arm, 3-year EFS was 77% in good responders and 60% in poor responders.

4. Discussion

This randomised paediatric trial has confirmed the hypothesis that etoposide-ifosfamide plus HD-MTX leads to significantly more good histologic responses than doxorubicin plus HD-MTX (56% versus 39%). We chose the histologic response as the main endpoint to evaluate the efficacy of preoperative chemotherapy because it is strongly predictive of subsequent outcome[2,4,5,19–23] and, in our treatment strategy,

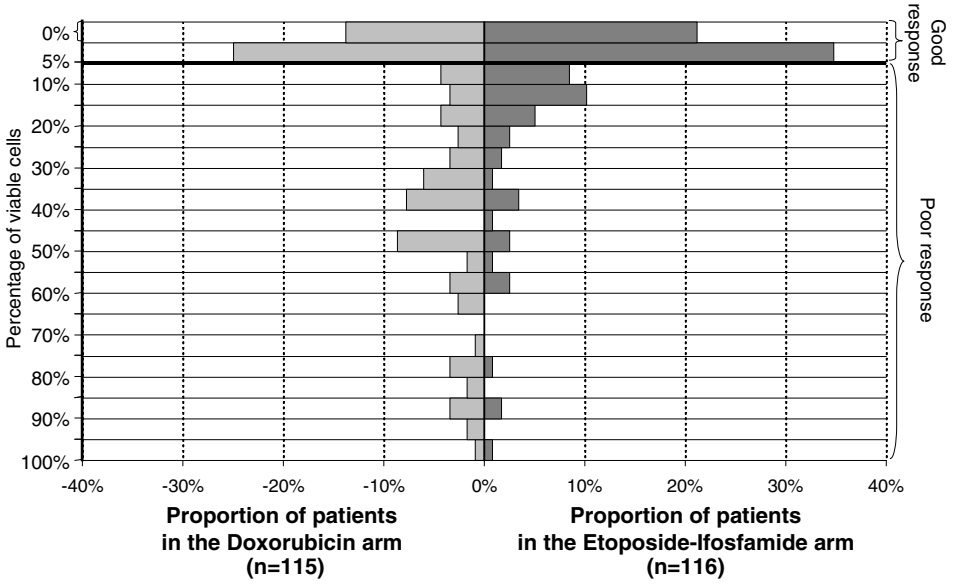

Fig. 3 – Histologic response by treatment arm. This information is available for 115/116 patients of doxorubicin arm and 116/118 patients of etoposide-ifosfamide arm. The mean percentage of residual viable cells was not recorded for three patients classified as poor responders.

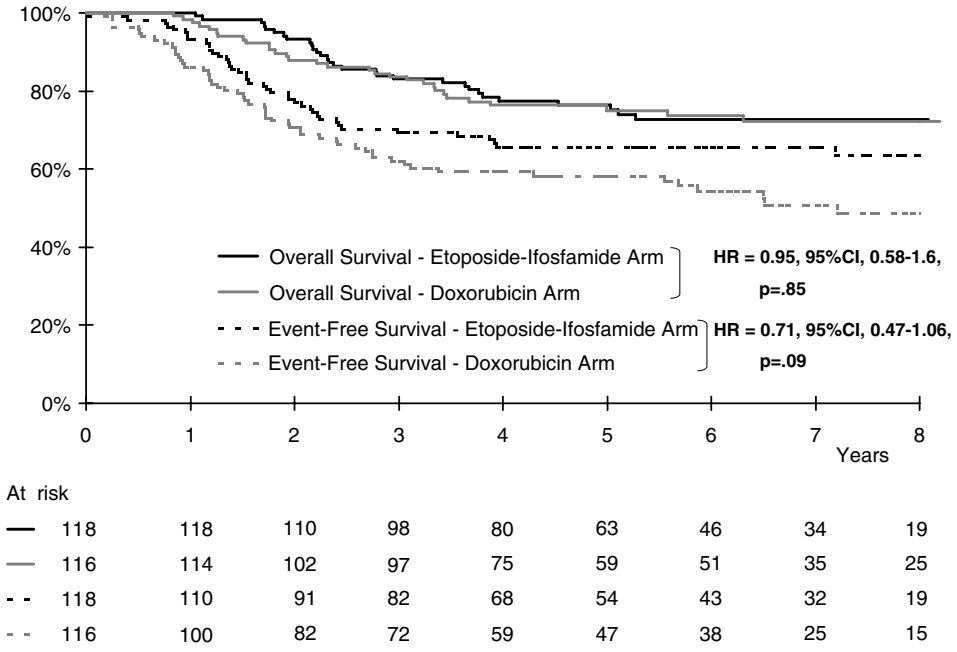

Fig. 4 – Overall (OS) and event-free (EFS) survival by treatment arm.

Table 2 – Outcome by treatment arm

Outcome	Treatment arm				*p*-value
	Doxorubicin		Etoposide-ifosfamide		
	Estimates	(95%CI)[a]	Estimates	(95%CI)	
Histologic response					
Good response	45/116		66/118		
	39%	(30–48%)	56%	(46–65%)	
Odds ratio of histologic failure[b]	1[c]		0.50	(0.30–0.84)	0.009
Event-free survival (EFS)					
Type of first event					
Local relapse	6		4		
Metastatic relapse	41		32		
Local and metastatic relapse	4		3		
Second malignancy	3[d]		2		
Toxic death	0		0		
Total number of events	54		41		
3-year EFS	62%	(53–71%)	69%	(61–78%)	
5-year EFS	58%	(49–67%)	66%	(57–74%)	
Hazard ratio of failure[b]	1[c]		0.71	(0.47–1.06)	0.09
Overall survival (OS)					
Cause of death					
Disease progression	29		29		
Second malignancy	2		1		
Total number of deaths	31		30		
3-year OS	84%	(76–89%)	83%	(75–89%)	
5-year OS	75%	(66–82%)	76%	(68–83%)	
Hazard ratio of death†	1[c]		0.95	(0.58–1.6)	0.85

a 95%CI: 95% confidence interval.
b Adjusted on centre category.
c Reference category.
d Four patients of the Doxorubicin arm developed a second malignancy, but one haematological malignancy occurred after a relapse and thus is not a first event.

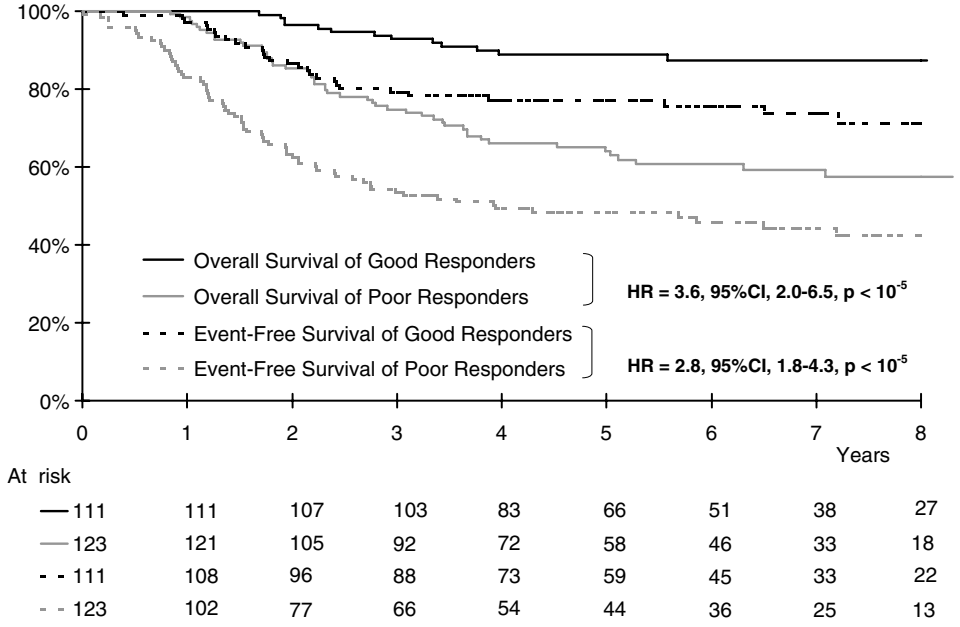

Fig. 5 – Overall (OS) and event-free (EFS) survival of the entire population according to histologic response.

we used a salvage treatment postoperatively for poor responders.

It is unlikely that the observed difference is related to the longer duration of preoperative chemotherapy since the number of courses is the same in both arms and the difference in median duration is only 1.6 weeks.

The external validity of our trial is good: one can estimate that about 75 patients under 20 years of age are diagnosed with an osteosarcoma each year in France,[24,25] leading to a total of 525 over 7 years; we have assessed for eligibility 486 of these patients (93%) and few patients with a non metastatic extremity osteosarcoma failed to enter into the trial.

The control arm may presently be considered as suboptimal as compared to cisplatin-containing regimen currently used nowadays. However, when the trial was designed in 1993, the superiority of cisplatin-containing regimen was not clearly demonstrated.[5]

The 56% of total or near total necrosis and the 64% necrosis > 90% observed in the etoposide-ifosfamide arm, as well as the EFS, compare favourably with the results obtained with regimens combining HD-MTX, doxorubicin and cisplatin, with or without ifosfamide.[1,2,20,22] In some of these publications, axial operable tumours and patients aged between 20 and 40 were also included but no difference in prognosis was reported between these categories of patients.

EFS was slightly greater in the etoposide-ifosfamide arm than in the doxorubicin arm, but the difference was not significant (HR = 0.71, 95% CI: 0.5 to 1.06). If the observed reduction of 29% were true, this would be clinically significant. The power to detect an improvement in EFS was low in our study due to the small number of patients and the current follow-up.

In the present trial, preoperative chemotherapy was based on a limited number of cytotoxic agents, the other drugs being reserved for postoperative treatment of poor responders. Salvage treatment of poor responders in the etoposide-ifosfamide arm with five cisplatin-doxorubicin courses led to a 60% 3-year EFS rate, which compares favourably with EFS rates observed among poor responders in other trials.[2,22,26]

Overall, acute toxicity was manageable in this paediatric multi-centre study. Particularly, no acute toxicity related death was observed contrary to more intensive regimens.[21,27] As expected, acute haematological toxicity was more frequent in the etoposide-ifosfamide arm. Unexpectedly, methotrexate-related hepatotoxicity was significantly less frequent in the etoposide-ifosfamide arm than in the doxorubicin arm.

Long-term toxicity will be reported separately later, since data are presently immature. Patients receiving 60 g/m^2 of ifosfamide should be carefully assessed for long-term renal function. At the present time, good responders who received HD-MTX and etoposide-ifosfamide courses alone are not exposed to the cardiotoxicity of doxorubicin nor to the ototoxicity of cisplatin. At 3 years of follow-up, they represent 43% of the patients in the etoposide-ifosfamide arm (56% good responders multiplied by 77% EFS at 3 years).

The risk of leukaemia associated with etoposide and doxorubicin has been demonstrated.[28] When the trial was initiated, the cumulative dose of etoposide equal to 1500 mg/m^2 administered in this protocol was wrongly considered safe. In this study, one patient developed M5-AML with a t(9;11)(p21–22;q23) translocation involving the MLL gene, after having received HD-MTX plus 350 mg/m^2 doxorubicin alone. An increased relative risk of second malignancy and particularly of leukaemia has been described after osteosarcoma, independently of treatment[28–30] and could partly explain the high absolute leukaemia rate observed in this series.

In conclusion, this trial has provided good evidence that the combination of etoposide-ifosfamide with HD-MTX led to a higher rate of good responses than doxorubicin.

About 43% of the patients in the etoposide-ifosfamide arm were event free at 3 years and had not received any doxorubi-

cin or cisplatin thus avoiding the risk of long-term cardio- and ototoxicity.

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The funding sources had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Conflict of interest statement

None declared.

Acknowledgements

Authors' contribution

The authors contributed to

- the conception and design of the trial as a member of the SFOP Osteosarcoma group (CK, JCG, HP, FP, PMB, MDT, NEW; CS, LB);
- the inclusion of patients (CK, JCG, HP, FP, PMB, MDT, NEW; CS, LB);
- the data management (ND);
- the review of pathology data (JMG);
- the review of radiological films (DV);
- the analysis (MCLD) and interpretation of the data (CK, MCLD, LB, MDT);
- the preparation of the manuscript (MCLD,CK, LB).

All the authors critically reviewed earlier drafts and have read and approved the final version of the above mentioned manuscript.

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