

Improvement in Histologic Response But Not Survival in Osteosarcoma Patients Treated With Intensified Chemotherapy: A Randomized Phase III Trial of the European Osteosarcoma Intergroup

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On behalf of MRC BO06 and EORTC 80931 collaborators and European Osteosarcoma Intergroup

- Background** Previous randomized controlled trials that used the two-drug chemotherapy regimen of cisplatin and doxorubicin as the conventional arm showed no evidence of benefit from an increase in the number of agents or the length of treatment. It was then proposed that survival could be improved by increasing the planned dose intensity of cisplatin and doxorubicin.
- Methods** Previously untreated patients with nonmetastatic, high-grade, central osteosarcoma of an extremity were randomly assigned to Regimen-C (conventional treatment with six 3-week cycles of cisplatin [100 mg/m² by 24-hour infusion] and doxorubicin [25 mg/m²/day by 4-hour infusion for 3 days]) or to Regimen-DI (intensified treatment with identical total doses of cisplatin and doxorubicin, planned as six 2-week cycles supported by granulocyte colony stimulating factor (G-CSF). Surgery was scheduled for week 6 in both arms. Primary and secondary outcome measures were overall and progression-free survival, respectively. Intention-to-treat analyses were performed using standard survival analysis methods. Landmark analyses were performed in patients with known surgical details and centrally reviewed histologic response. All statistical tests were two-sided.
- Results** Between May 1993 and September 2002, treatment was randomly allocated to 497 eligible patients. Six cycles of chemotherapy were completed by 78% of patients in Regimen-C and 80% of patients in Regimen-DI. The delivered preoperative median dose intensity of cisplatin was 86% in Regimen-C and 111% in Regimen-DI (as the percentage of that planned for the conventional regimen). Postoperative median dose intensity of cisplatin was 82% in Regimen-C and 110% in Regimen-DI (the corresponding figures for doxorubicin dose intensity were similar). Regimen-DI was associated with lower risks of severe leucopenia and neutropenia and higher risks of thrombocytopenia and mucositis. Good histologic response (>90% tumor necrosis) was observed in 36% of Regimen-C patients and 50% of Regimen-DI patients ($P = .003$, χ^2 test). There was no evidence of a difference in overall survival (hazard ratio [HR] = 0.94, 95% CI = 0.71 to 1.24; $P = .64$) or progression-free survival (HR = 0.98, 95% CI = 0.77 to 1.24; $P = .83$). Landmark analyses showed similar results.
- Conclusions** Planned intensification of chemotherapy with cisplatin and doxorubicin increased received dose intensity and resulted in a statistically significant increase in favorable histologic response rate, but not in increased progression-free or overall survival. Our results call into question the use of histologic response as a surrogate outcome measure in trials of this disease.

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See "Notes" following "References."

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CONTEXT AND CAVEATS

Prior knowledge

Chemotherapy has improved outcomes for patients with osteosarcoma such that 50%–70% of them are alive 5 years after diagnosis. However, in recent trials, treatments in which the number of chemotherapeutic agents or the duration of chemotherapy was increased did not improve patient survival compared to conventional chemotherapy.

Study design

This is a randomized clinical trial comparing two treatment regimens with overall and progression-free survival as the clinical endpoints.

Contribution

This trial investigated whether increasing the planned dose intensity of the chemotherapeutic agents cisplatin and doxorubicin would improve outcomes compared to conventional treatment with these drugs. The investigators found that increased dose intensity, while improving histologic response, did not prolong patient survival.

Implications

Testing of additional therapeutic strategies will be required to improve survival of patients with osteosarcoma, and histologic response may not be a valid surrogate outcome in osteosarcoma trials.

Limitations

Due to the rarity of osteosarcoma, this trial took a long time to recruit and mature, and it involved many countries with different standard approaches to chemotherapy and surgery.

During the last three decades, 5-year survival of patients with localized high-grade osteosarcoma has risen from less than 20% to 50%–70%, and parallel advances in conserving surgical techniques have led to limb salvage rates of more than 75% (1). These improved outcomes followed the introduction of effective adjuvant and neoadjuvant chemotherapy (2–11). At present, the four principal active drugs for osteosarcoma are cisplatin (12,13), doxorubicin (14), high-dose methotrexate (15,16), and ifosfamide (17,18), but the most effective combination of these agents is unknown (4–11).

The European Osteosarcoma Intergroup (EOI) was formed in 1982 to conduct randomized controlled trials for patients with osteosarcoma. The first EOI randomized controlled trial (Medical Research Council [MRC] BO02, European Organization for Research and Treatment of Cancer [EORTC] 80831) (6) compared six cycles of a two-drug regimen (cisplatin and doxorubicin) (19) with four cycles of a three-drug regimen (cisplatin, doxorubicin, and high-dose methotrexate). In 198 patients with primary nonmetastatic limb osteosarcoma, the two-drug regimen was associated with a statistically significant increase in progression-free survival at 5 years (57% versus 41%, hazard ratio [HR] = 0.63 (95% confidence interval [CI] = 0.42 to 0.94). The second EOI randomized controlled trial (MRC BO03, EORTC 80861) (7) compared an 18-week, two-drug regimen consisting of cisplatin and doxorubicin with a 47-week multidrug regimen consisting of high-dose methotrexate, doxorubicin, cisplatin, bleomycin, cyclophosphamide, and actinomycin-D that was based on the Rosen

T-10 protocol (18). Between 1986 and 1993, 391 eligible patients with primary nonmetastatic limb osteosarcoma were randomly assigned to these two treatments. No difference was observed in progression-free survival (HR = 1.01, 95% CI = 0.77 to 1.33) or overall survival, with 5-year progression-free survival and overall survival of 44% and 55%, respectively, in both arms.

In experimental animal models for the treatment of chemosensitive tumors, most cytotoxic drugs exhibit a sigmoidal dose-response curve (20) with lag, linear, and plateau phases. Increasing total dose or dose intensity such that drug concentration increases to higher values within the linear phase of the dose-response curve should minimize drug resistance and maximize effective cell kill (21). In the clinical setting, the nature of dose-response curves are unknown, and, in particular, the slopes of the linear phase and the plateau doses have not been determined.

Clinical studies in various adult and childhood malignancies indicated that dose intensity may be important in determining survival: retrospective studies in breast cancer (22), Hodgkin lymphoma (23), non-Hodgkin lymphoma (24,25), and neuroblastoma (26) showed a positive association between planned dose intensity and survival in conventional dosing schedules. Evidence as to whether increasing planned dose intensity above conventional levels by dose compression improves outcome has been evolving in a number of malignancies (27–30). More recently, this concept of increasing dose intensity has been referred to as “dose density.” The hypothesized advantage of dose-dense chemotherapy is that compressing conventional schedules of drug administration can achieve greater efficacy by minimizing regrowth of tumor cells between treatment cycles (31).

Several retrospective studies have identified dose intensity as a potentially important determinant of outcome in patients treated for osteosarcoma. In a review of 16 studies, Smith et al. (32) found a strong relationship between planned doxorubicin dose intensity and histologic tumor necrosis. Other retrospective studies concluded that doxorubicin dose (33) or planned high-dose methotrexate intensity (34,35) influenced outcome. The EOI investigated the impact of received dose intensity on the conventional two-drug cisplatin and doxorubicin regimen given every 3 weeks (36). This retrospective analysis of trial data failed to demonstrate any benefit for those patients who received this regimen most intensively. However, both overall survival and progression-free survival were lowest for patients receiving the lowest dose intensity, and progression-free survival was lower for those who received between one and five treatment cycles compared to those who received all six cycles.

Previous EOI trials showed no additional benefit from increasing the number of agents or length of treatment, and therefore, the two-drug cisplatin and doxorubicin remained our standard. It was hypothesized that a further increase in the planned dose intensity of cisplatin and doxorubicin would improve outcome. A pilot study demonstrated the feasibility of increasing the dose intensity of the two-drug regimen by 50%, by using granulocyte colony-stimulating factor (G-CSF) to shorten the treatment cycle from 3 to 2 weeks (37). This demonstration has formed the basis of the trial (MRC BO06/EORTC 80931) reported here. To our knowledge, this is the first randomized trial of the effectiveness of increased dose intensity in the treatment of high-grade osteosarcoma.

Patients and Methods

Trial Design

This was an open-label randomized controlled trial with the primary outcome measure of overall survival (time to death from any cause) and a secondary outcome measure of progression-free survival, i.e., time to nontumor death or any relapse or recurrence including distant metastases (but not including local disease progression before primary surgery). For the trial, 165 events were planned to detect an improvement of 15% in 5-year survival (55%–70%, HR = 0.6) with 90% power and a two-sided statistical significance level of 5%. Randomizations were performed separately and centrally at the two trials offices (Medical Research Council Clinical Trials Unit [MRC CTU] and EORTC Data Center). Minimization was performed with two stratification factors: center and age (0–16 or ≥ 17 years).

Patients

Patients aged 40 years or less with a histologically confirmed diagnosis of high-grade osteosarcoma in an extremity long bone (38) were eligible for the trial (39,40). An EOI pathologist reviewed each diagnosis and assigned histologic subtype. Patients with paraosteal, periosteal, Paget-related, or radiation-induced osteosarcoma were ineligible. Also excluded were patients with prior malignancy, any chemotherapy before trial entry, reduced glomerular filtration rate (< 60 mL/min/1.73 m²), cardiac dysfunction, or raised bilirubin. In addition, to be eligible, patients needed to commence chemotherapy within 28 days after biopsy, with normal leukocyte ($\geq 3.5 \times 10^9/L$) and platelet ($\geq 100 \times 10^9/L$) counts. Informed consent was obtained according to local requirements.

Initial staging investigations included plain radiography of tumor and chest, computerized tomography (CT) or magnetic resonance image of affected limb, CT scan of thorax, and isotope bone scan. Patients with demonstrable metastases were ineligible, but equivocal radiology results without confirmed metastases did not render patients ineligible.

Patients had full assessment at diagnosis of hematologic and biochemical parameters. This assessment included determination of hemoglobin levels, total and differential white blood cell counts, platelet counts, and examination of blood film. Plasma levels of creatinine, urea, sodium, potassium, chloride, calcium, magnesium, and phosphate were determined. Liver function tests included measurement of bilirubin and alkaline phosphatase and transaminase activity. Renal function was assessed by either ⁵¹chromium-EDTA or ⁵¹chromium-DTPA isotopic renal clearance. Audiometry was performed according to local practice. Cardiac function was assessed by echocardiogram or an equivalent test.

Quality Assurance

The trial was run from the MRC CTU, London, United Kingdom (formerly MRC Cancer Trials Office, Cambridge, United Kingdom) and the EORTC Data Center, Brussels, Belgium. Data were collated for analysis at MRC CTU. The trial was overseen by the Trial Management Group and reviewed on three occasions by an independent Data Monitoring Committee. No formal stopping rules were specified. On the occasion of each review, the Data Monitoring Committee recommended that the trial continue. This trial was con-

ducted in compliance with the Declaration of Helsinki, and the protocol was approved by the appropriate Research Ethics Committees.

Chemotherapy

As planned, the conventional two-drug regimen (Regimen-C) consisted of six 3-week cycles, each commencing with administration of doxorubicin (25 mg/m²) by 4-hour infusion (repeated on days 2 and 3) and cisplatin (100 mg/m²) by 24-hour infusion, with surgery planned between cycles 2 and 3. Regimen-DI consisted of six cycles of treatment with the same doses of cisplatin and doxorubicin as in the conventional regimen, but with cycles planned to commence every 2 weeks. Patients treated with this regimen were supported by G-CSF (5 μ g/kg daily) by subcutaneous injection on days 4–13 of each cycle). Surgery was planned between cycles 3 and 4. For both regimens, cisplatin infusion was preceded by 4 hours of prehydration followed by a 24-hour posthydration schedule, which included a forced mannitol diuresis. It was recommended that cisplatin be given as a 24-hour infusion diluted in isotonic saline with added potassium chloride and mannitol. In both arms, the surgery window was 14 days in duration. G-CSF was lenograstim (Amgen, United Kingdom) or filgrastim (Chugai, United Kingdom) according to local arrangements. The complete schedules for both regimens are shown in Fig. 1.

Toxicity Monitoring and Dose Modification. Height (cm), weight (kg), surface area (m²), glomerular function, and levels of creatinine, sodium, potassium, calcium, magnesium, chloride, phosphates, alkaline phosphatase, bilirubin, and transaminases were determined before each cycle according to local practice. Blood counts were obtained before each cycle and at the expected nadir of the count (day 10 in Regimen-C, day 8 in Regimen-DI). Doses could be delayed or reduced according to specific criteria as follows: Dose reductions of 20% were advised for patients with febrile neutropenia requiring antibiotics or platelet transfusion. Delay was advised where neutrophil counts were less than $1 \times 10^9/L$ and/or platelets were less than $100 \times 10^9/L$, amended in 1997 to platelets $75 \times 10^9/L$. Toxicity was graded using the World Health Organization (WHO) toxicity coding scheme (41). Delay or dose reduction was advised for renal toxicity or mucositis (WHO grade 3–4 in both cases). Discontinuation of cisplatin was advised if the glomerular filtration rate fell below 60 mL/min/1.73 m² for more than 1 week or if grade 3–4 neurotoxicity or symptomatic ototoxicity was observed. Cardiac function was assessed by echocardiogram or equivalent before treatment and before cycles 3–6. The Children's Cancer Study Group anthracycline administration guideline (42) was adopted during the trial to provide more consistency to the management of doxorubicin-induced cardiotoxicity.

Calculation of Dose Intensity. Preoperative, postoperative, and overall dose intensity were each calculated for cisplatin and doxorubicin according to the protocol expectations for Regimen-C and Regimen-DI using the formula

$$\text{Dose intensity} = \frac{\text{Actual dose given/Expected dose given}}{\text{Actual duration of chemotherapy/Expected duration of chemotherapy}}$$

Calculation of expected dose and time was based on protocol doses with adjustments made for reported changes in body surface area during treatment, as indicated by measurements conducted

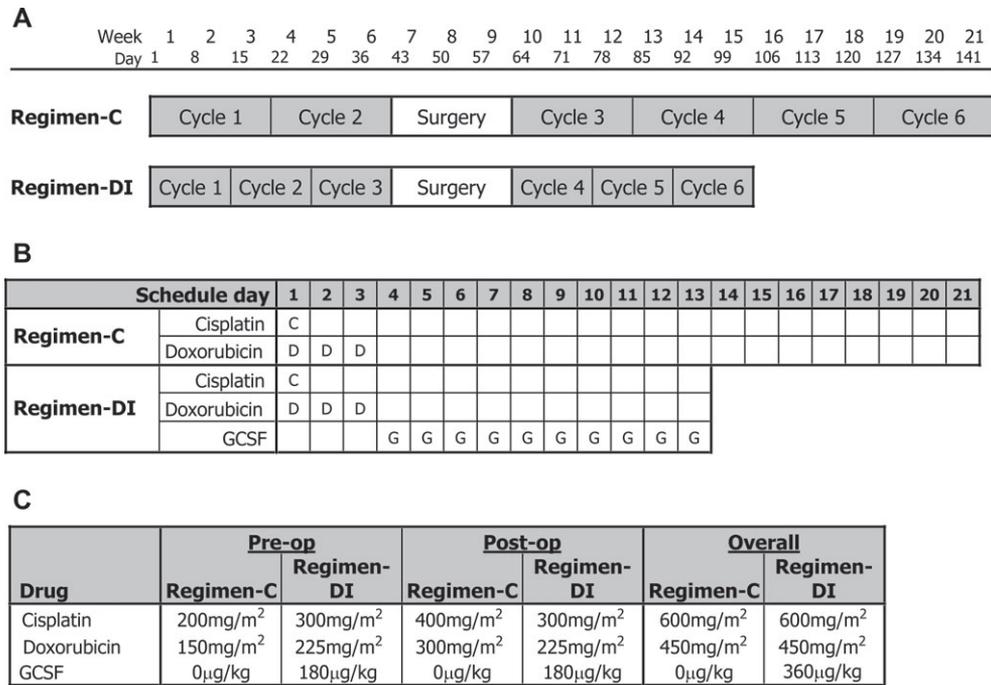


Fig. 1. Schedule of drug treatment and surgery and planned dosage in the trial. **A)** Schedule of drug treatment cycles and surgery for the conventional regimen (Regimen-C) and the dose-intensive regimen (Regimen-DI) that were compared in the trial. **B)** Schedule of drug doses within each cycle. In both regimens, C = administration of cisplatin as a 100 mg/m² 24-hour infusion, D = administration of doxorubicin as a

25 mg/m² 4-hour intravenous infusion, and G = granulocyte colony-stimulating factor (GCSF) given as a 5 μg/kg injection. Cisplatin infusion was preceded by 4 hours of predehydration followed by a 24-hour posthydration schedule, which included a forced mannitol diuresis. **C)** Planned total doses of each drug according to regimen in preoperative, postoperative, and full period of treatment.

before each cycle was administered. In these calculations, the length of the final cycle was considered to be the full expected length (not the time to the last dose) to reflect recovery time. Preoperative time was taken as the period from the start of chemotherapy until the day of surgery or, if surgery was not performed, until the end of last cycle. Postoperative time was taken as the period from the start of postoperative chemotherapy until its completion. Overall duration was calculated in two ways: as the full duration from the start of chemotherapy until the end of chemotherapy including the surgical period or similarly but excluding the surgical period.

Surgery

Patients were clinical and radiologically assessed for response in the week before surgery. Local progression was defined as increase in tumor size or worsening pain and systemic progression as the development of distant metastases. Patients with local progression alone were advised to have surgery and continue on protocol; the appearance of metastases was deemed a progression-free survival event, and such patients were treated off protocol.

Surgery was planned for day 42 in both arms or as soon thereafter as hematologic recovery allowed. Decisions about the type of planned surgery, i.e., limb sparing or amputation, were made by clinical teams. Surgical margins were defined as radical, wide, marginal, or intralesional. Further details about surgery will be published separately.

Histologic Response Assessment

Resected tumor specimens were assessed for histologic response to preoperative chemotherapy (43). Using the definitions employed

in the two previous EOI trials, tumor necrosis more than 90% was defined as “good” histopathologic response; 10% or more viable tumor after chemotherapy was defined “poor”. As tumors with a substantial chondroblastic component are intrinsically less responsive to chemotherapy, the extent of chondroblastic differentiation was assessed using a standard method of microscopic examination to stratify cases. Tumors in which there was more than 30% volume of chondroblastic differentiation relative to tumor volume were defined as chondroblastic. Specimens were reviewed centrally by EOI pathologists wherever possible.

End of Treatment and Off-treatment Monitoring

Full radiologic and toxicity assessment was advised following completion of treatment. Investigators were advised to perform clinical follow-up with chest radiography monthly for the first 6 months after treatment, every 2 months until the end of year 1, every 3 months during year 2, every 4 months during year 3, and every 6 months until year 5. After 5 years, follow-up was annual. Cardiac function was assessed at 1, 3, and 5 years by echocardiography or equivalent local practice.

Statistical Analyses

Analyses were performed on a modified intention-to-treat basis: all patients were included in the analysis except for patients determined to be histologically ineligible during central pathology review, which was performed without reference to treatment allocation. These patients were excluded because it was independently confirmed that they were ineligible before randomization and should not have been entered. Patients who were found after random

assignment to have violated other eligibility criteria were included in the analysis because such assessment was not blind to treatment allocation. Baseline characteristics of the patients and their tumors were described but not formally tested for differences across arms.

All tests were two-sided. No formal adjustments were made for multiple testing. Confidence intervals were calculated at the 95% level. Histologic response to preoperative chemotherapy was quantified using the chi-square test for association and toxicities using relative risks (RRs). Time-to-event data were summarized using hazard ratio and Kaplan–Meier plots and compared with log-rank tests. All comparisons including relative risks and hazard ratios were relative to Regimen-C; therefore, a hazard ratio of less than 1.0 indicated an advantage of Regimen-DI. For time-to-event calculations, time was from randomization unless specified. Adjusted hazard ratios were obtained using Cox regression models; the assumption of proportionality was checked both visually and by using tools in the Stata software. Tests for heterogeneity of effect across groups were tested with chi-square tests for interaction. Statistical analyses were performed using Stata 9 software (Stata Corporation, College Station, TX).

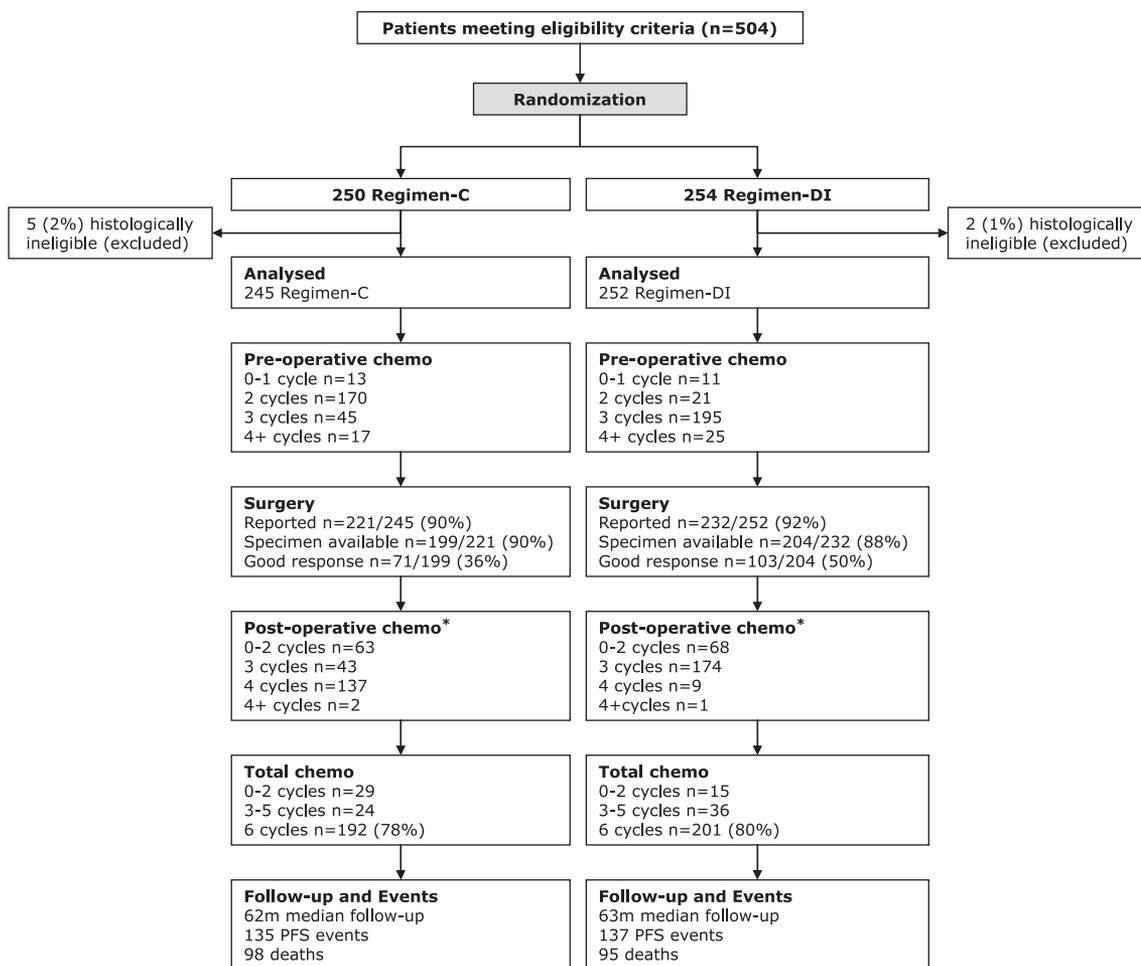
Exploratory and Landmark Analyses. The purpose of the landmark analyses was to allow for comparison of treatment arms

accounting for histologic response, which was not known until after surgery, the primary treatment, had been performed. For patients included in the landmark analyses, both surgical details and histologic response had to be ascertained and time was taken as starting from 60 days after randomization at which time surgery should have been performed and histologic response known. Histologic response was unobtainable for some patients. Therefore, exploratory survival models were constructed using the landmark approach to look at how histologic response (good, poor, unobtainable, or no surgery) affected outcome. Additionally, a series of univariate and multivariable Cox regression models were constructed to examine the effect of overall and preoperative dose and dose intensity on overall survival. Finally, sensitivity analyses were performed on overall survival and progression-free survival for the whole population of all 504 randomly assigned patients including those patients excluded for reasons of prerandomization ineligibility.

Results

Accrual, Patient Characteristics, and Follow-up

Between May 1, 1993, and September 30, 2002, 504 patients with presumed nonmetastatic operable osteosarcoma were enrolled—292 through the MRC CTU (United Kingdom, Argentina, and Chile)



*Includes as zero cycles patients who did not start chemotherapy and patients who did not report surgery

Fig. 2. Trial flow diagram (Consolidated Standards of Reporting Clinical Trials [CONSORT] diagram).

Table 1. Baseline characteristics*

Baseline characteristic	Allocated treatment					
	Regimen-C		Regimen-DI		Overall	
	N	%	N	%	N	%
Eligibility†						
Eligible	241	96	249	98	490	97
Ineligible—pathology	4	2	1	0	5	1
Ineligible—other	4	2	3	1	7	1
Ineligible—pathology and other	1	0	1	0	2	0
Sex‡						
Male	144	60	149	59	293	59
Female	98	40	103	41	201	41
Age (y)						
≤16	158	64	161	64	319	64
>16	87	36	91	36	178	36
Median (quartiles)	15 (12–18)		15 (13–18)		15 (12–18)	
Minimum/maximum	4/38		5/41		4/41	
Site						
Femur	143	59	153	61	296	60
Tibia	60	25	56	22	116	24
Fibula	13	5	12	5	25	5
Humerus	22	9	26	10	48	10
Radius	3	1	2	1	5	1
Ulna	0	0	1	0	1	0
Missing	4	–	2	–	6	–
Location within bone						
Proximal	93	39	97	39	190	39
Midshaft	8	3	4	2	12	2
Distal	139	58	149	60	288	59
Missing	5	–	2	–	7	–
Pathology						
Common type	131	60	152	68	283	64
Chondroblastic	25	12	26	12	51	12
Fibroblastic	9	4	6	3	15	3
Osteoclast rich	2	1	7	3	9	2
Anaplastic	9	4	12	5	21	5
Small cell osteo	3	1	2	1	5	1
Telangiectatic	22	10	7	3	29	7
Other type	16	7	12	5	28	6
Missing§	28	–	28	–	56	–
Total included	245	100	252	100	497	100
Ineligible	5	–	2	–	7	–
Total randomly assigned	250		254		504	

* Regimen-C = conventional regimen; Regimen-DI = dose-intensive regimen. Percentages may not add to 100% because of rounding.

† Randomly assigned patients were excluded only if determined not to meet the pathology criteria on central pathology review.

‡ Sex was missing for three patients on Regimen-C.

§ Histology was determined on central pathology review using the initial biopsy sample or the resected specimen. No samples were available for 43 patients. One or both of these were available for 461 (91%) of randomly assigned patients. In 10 of these patients, the material could not be assessed, and class was not available for 10 further patients. Patients were included in the analyses unless they were shown to be pathologically ineligible. Therefore, 497 patients are included.

and 212 through the EORTC (including Netherlands, Saudi Arabia, Belgium, and Denmark) (full details are presented in the Appendix). A Consolidated Standards of Reporting Trials flow diagram of the trial is presented in Fig. 2. Pathologic review identified seven patients as ineligible due to inappropriate histologic diagnoses, and these were excluded from further analyses. Therefore, 497 patients (245 assigned to Regimen-C and 252 assigned to Regimen-DI) were analyzed, including 36 patients who were not centrally reviewed. Seven patients were found to not fulfill eligibility criteria after random assignment (three due to the presence of metastases, three because their osteosarcoma was at an incorrect site, and one due to renal insufficiency) but were included

in the analyses. The baseline characteristics of the 490 eligible patients are shown in Table 1. More than 60% were 16 years old or younger, and 60% were male. Distal femur was the most common site of osteosarcoma. Common-type osteosarcoma was the most frequent histologic subtype, followed by chondroblastic osteosarcoma. Other subtypes occurred infrequently. The treatment groups were balanced in terms of tumor site, location within the bone, and a combination of site and location (data not shown).

With reverse Kaplan–Meier censoring (44), median follow-up time was 62 months (range 0–126 months). Of the patients last reported alive, 91%, 68%, and 44% had follow-up of ≥1, 3, and 5 years, respectively. The corresponding percentages were similar in

Table 2. Chemotherapy and surgery data*

Chemotherapy and surgery	Allocated treatment			
	Regimen-C		Regimen-DI	
	N	%	N	%
Given intended number of cycles				
Preoperatively	170	69	195	77
Postoperatively	137	54	174	71
Overall	192	78	201	80
Reason for terminating chemotherapy				
Treatment completed	189	79	201	82
Disease progression	11	5	8	3
Excessive toxicity	12	5	17	7
Treatment refusal	12	5	8	3
Other reason	16	7	10	4
Not available	0	–	2	–
Histologic response†				
Good response	71	36	103	50
Poor response	128	64	101	50
Response unknown	22	–	28	–
Surgery not reported	24	–	20	–
Surgery performed				
Limb salvage	164	74	170	73
Amputation	38	17	46	20
Disarticulation	9	4	10	4
Rotation plasty	10	5	6	3
No surgery reported	24	–	20	–
Total included	245	100	252	100

* Regimen-C = conventional regimen; Regimen-DI = dose-intensive regimen.

† Good response is ≤10% viable tumor; poor response is >10% viable tumor.

both treatment groups. Deaths and progression-free survival events were reported in 193 (39%) and 272 (55%) patients, respectively.

Chemotherapy

Among eligible patients, 486 (98%) started trial chemotherapy, most within 1 day of random assignment. Figure 1 shows preoperative and postoperative chemotherapy cycles of Regimen-C (control regimen) and regimen-DI (dose-intensive regimen) and the planned schedule of doses (of cisplatin, doxorubicin, and G-CSF) within a cycle for the two regimens. The planned number of preoperative cycles was administered to 170 (69%) and 195 (77%) patients allocated to Regimen-C and Regimen-DI, respectively, and 192 (78%) and 201 (80%) patients received six cycles of Regimen-C and Regimen-DI, respectively (Table 2). The majority (80%) of patients stopped chemotherapy on completion of the protocol treatment, although 24 (10%) and 25 (10%), in Regimen-C and Regimen-DI, respectively, stopped prematurely due to excessive toxicity or patient choice. Three deaths occurred during the protocol treatment period, all among patients allocated to Regimen-DI. One patient who died received a very large, nonprotocol dose of cisplatin during cycle 1. G-CSF was administered to 20 (8%) of patients undergoing Regimen-C and to 244 (99%) of patients undergoing Regimen-DI. Figure 3, A, depicts time to stopping trial chemotherapy and shows how the time of chemotherapy was shorter for patients allocated Regimen-DI.

Nearly all (468 or 97%) the patients who had chemotherapy experienced severe (grade 3–4) toxicity (Table 3). Regimen-DI was

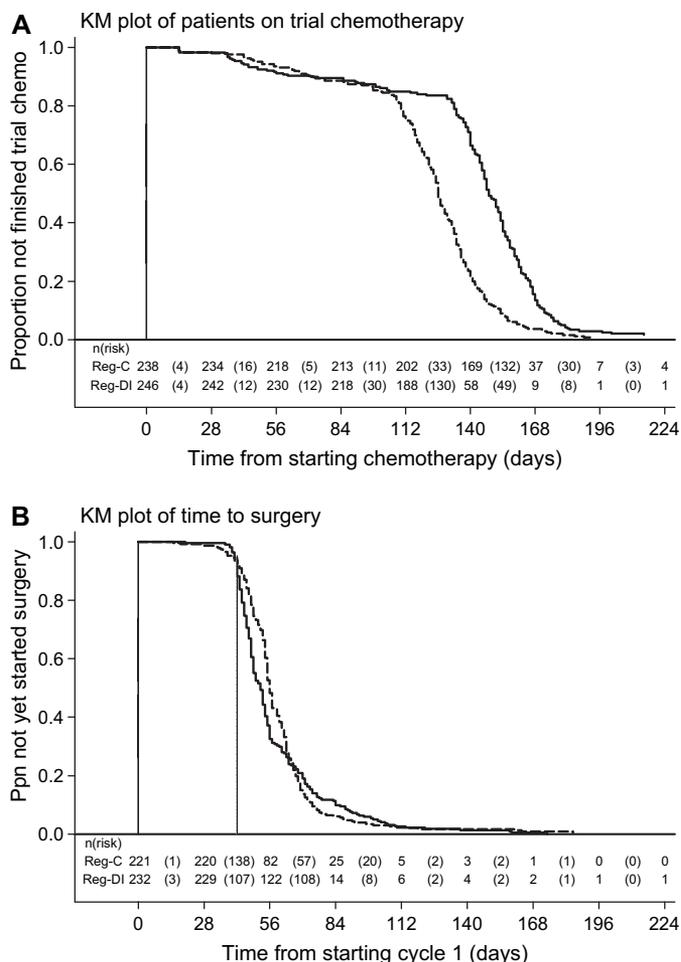


Fig. 3. Kaplan–Meier analysis of time from randomization to trial milestones. The proportion of patients in the conventional regimen (Regimen-C [solid line]) and the dose-intensive regimen (Regimen-DI [dashed line]) not yet having completed chemotherapy (A) and not yet having completed surgery if surgery was eventually performed (B) are shown. Surgery was expected at 42 days.

associated with lower risk of severe leucopenia (RR = 0.85, 95% CI = 0.77 to 0.95) and neutropenia (RR = 0.83, 95% CI = 0.76 to 0.89) and higher risk of thrombocytopenia (RR = 1.33, 95% CI = 1.17 to 1.52) and mucositis (RR = 1.30, 95% CI = 0.99 to 1.70). A small increase in ototoxicity was reported for patients on Regimen-DI. Table 4 shows the number of, and reasons for, dose reductions of 20% or greater of either drug and delays longer than 3 days in the 2639 reported cycles. There were more patients with at least one delay on Regimen-DI than on Regimen-C (190 patients on Regimen-C versus 227 patients on Regimen-DI, $\chi^2_1 = 15.71$, $P < .001$) and more delayed cycles on the intensive regimen (685 delayed cycles in Regimen-DI versus 420 delayed cycles in Regimen-C ($\chi^2_1 = 84.33$, $P < .001$)). Hematologic toxicity was reported to cause more delays on Regimen-DI (205 (15%) delayed cycles affecting 128 patients) than Regimen-C (104 (8%) delayed cycles affecting 68 patients). Dose reductions of cisplatin of more than 20% occurred in 162 (13%) cycles in Regimen-C and in 146 (11%) cycles in Regimen-DI; doxorubicin was reduced in 145 (11%) cycles in Regimen-C and in 147 (11%) cycles in Regimen-DI. Thus, the dose reduction of the two drugs was similar when

Table 3. Grade 3 or 4 toxicity during protocol chemotherapy*

Type	Regimen-C		Regimen-DI		RR (95% CI)†	χ ² , P value
	N	%	N	%		
WBC‡	193	81	170	69	0.85 (0.77 to 0.95)	9.27, <.001
Platelets‡	137	58	189	77	1.33 (1.17 to 1.52)	20.42, <.001
Neutrophil‡	220	92	188	76	0.83 (0.76 to 0.89)	23.44, <.001
Nausea	113	48	131	53	1.12 (0.94 to 1.33)	1.50, .22
Mucositis	64	27	86	35	1.30 (0.99 to 1.70)	3.69, .06
Infection	65	27	61	25	0.91 (0.67 to 1.23)	0.40, .53
Neurologic	0	0	2	1	–	1.94, .16
Ototoxicity	1	0	7	3	6.8 (0.84 to 54.84)	4.40, .04
Cardiac	6	3	2	1	0.32 (0.07 to 1.58)	2.17, .14
Any toxicities	232	97	236	96	0.98 (0.95 to 1.02)	0.90, .34

* Regimen-C = conventional regimen; Regimen-DI = dose-intensive regimen; WBC = white blood cell. Missing data (Regimen-C, Regimen-DI): WBC 2, 0; platelets 2, 0; neutrophil 2, 0; nausea 3, 0; mucositis 3, 1; infection 3, 1; neurologic 3, 1; ototoxicity 3, 2; cardiac 3, 1; other toxicities 5, 0; all toxicities 2, 0.

† RR = relative risk; CI = confidence interval.

‡ WBC, platelet, and neutrophil toxicity based on nadir counts before, during, and after each cycle.

compared across the same treatment group. Data pertaining to long-term cardiac function will be reported in detail elsewhere.

Received Dose and Dose Intensity Analysis

Preoperative, postoperative, and overall received dose and relative dose intensity of cisplatin and doxorubicin for a given regimen were calculated (Fig. 4). We plotted received dose intensity against received total dose in individual patients for each drug and allocated treatment. Overall, the scatter plots show that Regimen-DI led to more higher doses of drug and greater dose intensity preoperatively, lower doses of drug but great dose intensity postoperatively, and so similar doses of drug but greater dose intensity overall. The clear scattering of values in each of the plots shows the deviation from the summary figures for each treatment and each phase of treatment.

Dose. The median standardized received cisplatin doses for Regimen-C and Regimen-DI were 565/600 (94%) and 593/600 (99%), respectively, and the median standardized received doxorubicin doses were 428/450 (95%) and 440/450 (98%), respectively (Table 5). Thus, overall, higher total doses of cisplatin and doxorubicin were delivered to patients allocated to the intensified regimen. The explanation may be that, while in both arms the median preoperative received dose for each drug was as planned, there was some evidence of greater postoperative dose reductions in Regimen-C compared to Regimen-DI.

Time. The median time from the start of chemotherapy to surgery was 52 and 56 days for Regimen-C and Regimen-DI, respectively. Including the surgical period, patients allocated to

Table 4. Reported reasons for calculated reductions and delays during treatment*

Deviation type	Delays of ≥3 days, No. (%)		Cisplatin reduction ≥20%, No. (%)		Doxorubicin reduction ≥20%, No. (%)	
	Regimen-C	Regimen-DI	Regimen-C	Regimen-DI	Regimen-C	Regimen-DI
Patients with deviations†						
At least one cycle affected	190 (80)	227 (92)	69 (29)	70 (28)	64 (27)	70 (28)
No cycles affected	48 (20)	19 (8)	169 (71)	176 (72)	174 (73)	176 (72)
Total	238	246	238	246	238	246
Cycles with deviations‡						
Yes, reason known	200 (16)	343 (25)	127 (10)	130 (10)	113 (9)	132 (10)
Yes, reason not known	220 (17)	342 (25)	35 (3)	16 (1)	32 (2)	15 (1)
No	862 (67)	672 (50)	1120 (87)	1211 (89)	1137 (89)	1210 (89)
Total	1282	1357	1282	1357	1282	1357
Reasons for deviations§						
Administrative	15 (8)	25 (7)	3 (2)	6 (5)	1 (1)	6 (5)
Hematologic	104 (52)	205 (60)	63 (50)	58 (45)	62 (55)	68 (52)
Renal	4 (2)	4 (1)	6 (5)	10 (8)	1 (1)	0 (0)
Ototoxicity	1 (1)	4 (1)	6 (5)	8 (6)	0 (0)	0 (0)
Infection	32 (16)	30 (9)	15 (12)	7 (5)	14 (12)	9 (7)
Other	36 (18)	66 (19)	19 (15)	14 (11)	23 (20)	31 (23)
Any combination	8 (4)	9 (3)	15 (12)	27 (21)	12 (11)	18 (14)
Total	200	343	127	130	113	132

* The reasons for deviations are only known where they were reported explicitly; no reasons have been deduced where a reduction or delay was calculated but not reported explicitly. Regimen-C = conventional regimen; Regimen-DI = dose-intensive regimen.

† % as percentage of all patients starting chemotherapy.

‡ % as percentage of all cycles administered.

§ % as percentage of cycles with known reason delay or reduction.

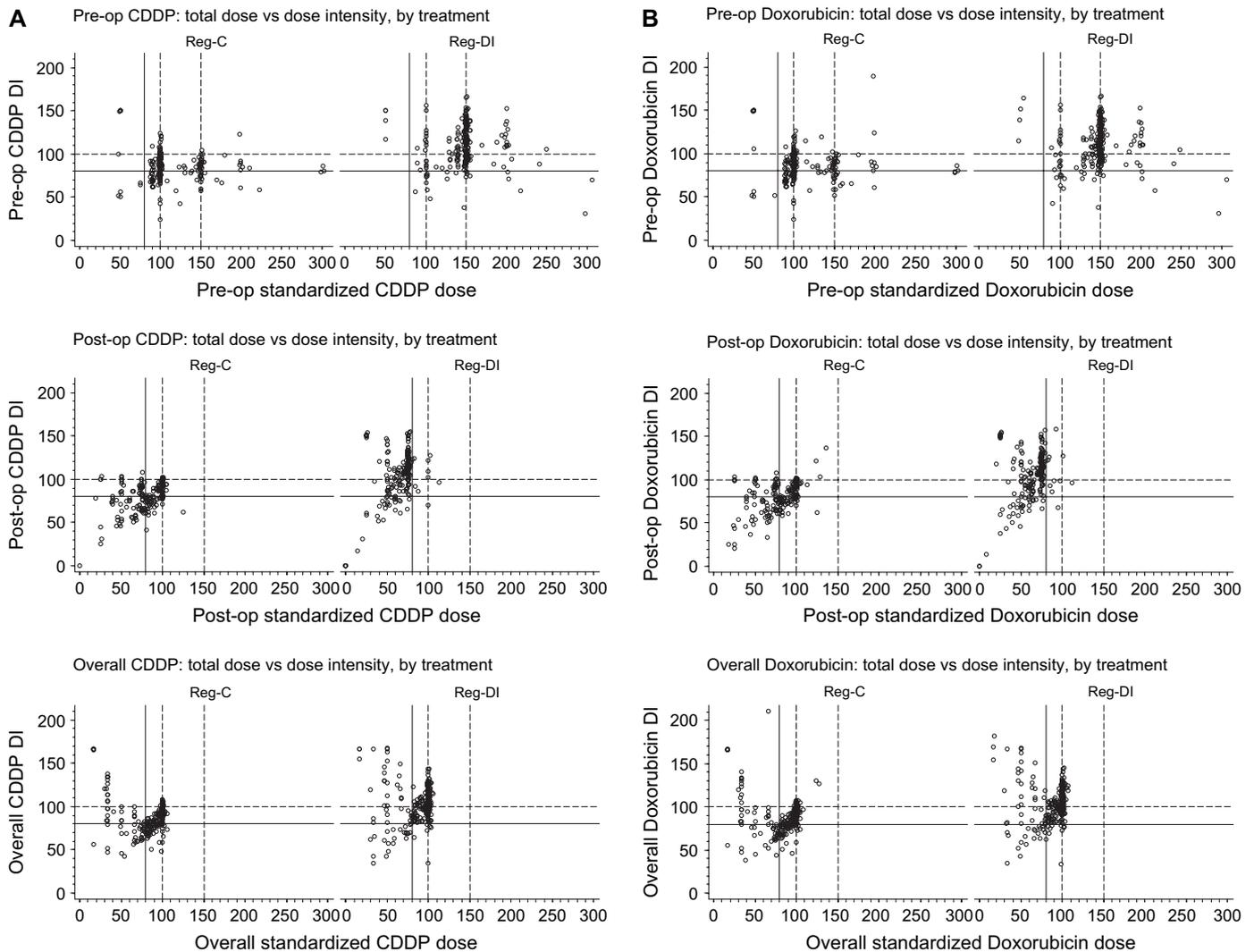


Fig. 4. Total dose and dose intensity for patients treated with chemotherapy for osteosarcoma relative to expectations of the conventional regimen. Scatter plots of standardized dose intensity versus standardized total dose of cisplatin (CDDP [A]) or doxorubicin (Dox [B]) for the preoperative (top panels), postoperative (middle panels), and the full course of treatment (lower panels) achieved for patients on the conven-

tional regimen (Regimen-C [open circles]) or the dose-intensive regimen (Regimen-DI [solid circles]). Dose and dose intensity values are given as a percent of the expectations of the control regimen. In each graph, the **top right quadrant** defined by **solid lines** marks out patients whose dose and dose intensity exceeded 80%. The **dashed lines** indicate the planned dose and dose intensity.

Regimen-C had a median time to completion of 155 days compared to 140 days planned, a relative increase of 10%. Regimen-DI had a median time to completion of 126 days compared to 98 days, an increase of 29%. Excluding the surgical period, patients allocated to Regimen-C had a median time to completion of 139 days compared to 126 days planned, a 10% increase, and Regimen-DI had an actual median time to completion of 109 days compared to 84 days planned, a 30% increase. Overall, the patients in Regimen-DI also experienced more delays than did patients in Regimen-C.

Dose Intensity. For purposes of comparison, dose intensities were calculated relative to the planned dose intensity for Regimen-C (100%). The median preoperative dose intensity achieved on Regimen-C was 86% for both cisplatin and doxorubicin and it was 111% on Regimen-DI for both drugs (Table 5). Thus, there was a 29% relative increase in actual preoperative dose intensity for Regimen-DI compared to the actual preoperative dose intensity of

Regimen-C. Postoperatively, the median cisplatin dose intensities on Regimen-C and Regimen-DI were 82% and 110%, respectively, a relative increase of 34% for Regimen-DI; the median dose intensities for doxorubicin were 83% and 111%, respectively, a relative 33% increase for Regimen-DI. In most cases observed dose intensity was below that planned. Excluding the surgery window, overall dose intensity achieved for cisplatin was 83% in Regimen-C and 108% in Regimen-DI, a relative increase of 29%, and for doxorubicin it was 83% and 109%, respectively, a relative increase of 31%. Thus, in each case, the received chemotherapy for Regimen-DI was more dose intensive than for Regimen-C. With Regimen-DI, overall dose intensity was 73% for doxorubicin and 72% for cisplatin of that expected for Regimen-DI protocol. Only seven Regimen-DI patients achieved a dose intensity of 150% and only 10 Regimen-C patients achieved a dose intensity of 100%. The observed reductions in dose intensity were due to reductions in treatment dose and delays in administering treatment.

Table 5. Summary of total dose and dose intensity by allocated regimen*

Timing	Regimen-C			Regimen-DI		
	Planned	Observed		Planned	Observed	
		Median	Quartiles		Median	Quartiles
Preoperative period						
Duration (days)	42	52	45–64	42	56	49–64
Cisplatin dose	200	200	199–218	300	300	289–301
Cisplatin DI						
Regimen-C plan	100†	86	76–93	150†	111	95–123
Regimen-DI plan	–	–	–	100‡	74	64–82
Doxorubicin dose	150	150	149–184	225	225	217–226
Doxorubicin DI						
Regimen-C plan	100†	86	77–94	150†	111	96–124
Regimen-DI plan	–	–	–	100‡	74	64–83
Surgical period						
Preoperative chemotherapy to surgery§ (days)	21	26	23–30	14	23	19–27
Surgery to postoperative chemotherapy (days)	14	18	14–22	14	17	14–21
Postoperative period						
Duration (days)	84	87	73–98	42	55	48–59
Cisplatin dose	400	335	288–400	300	296	219–300
Cisplatin DI						
Regimen-C plan	100†	82	72–93	150†	110	93–121
Regimen-DI plan	–	–	–	100‡	73	62–81
Doxorubicin dose	300	253	217–299	225	221	165–225
Doxorubicin DI						
Regimen-C plan	100†	83	73–95	150†	111	93–121
Regimen-DI plan	–	–	–	100‡	74	62–81
Overall						
Duration including surgery (days)	140	155	144–168	98	126	112–138
Duration excluding surgery (days)	126	139	129–150	84	109	97–120
Cisplatin dose	600	565	465–600	600	593	493–600
Cisplatin DI¶						
Regimen-C plan	100†	83	75–92	150†	108	95–122
Regimen-DI plan	–	–	–	100‡	72	63–82
Doxorubicin dose	450	428	354–449	450	440	373–450
Doxorubicin DI¶						
Regimen-C plan	100*	83	75–92	150†	109	94–122
Regimen-DI plan	–	–	–	100‡	73	62–81
G-CSF dose	–	0	0–0	–	9202	(7900–10598)

* Regimen-C = conventional regimen; Regimen-DI = dose-intensive regimen; G-CSF = granulocyte colony-stimulating factor.

† Compared to expectations of Regimen-C.

‡ Compared to expectations of Regimen-DI.

§ Time from first day of last preoperative chemotherapy cycle to day of surgery.

|| Time from day of surgery to first day of postoperative chemotherapy.

¶ Overall dose intensity was calculated using the overall duration including the surgical period; the surgical period was not included in the preoperative or postoperative DI calculations.

Surgery

Surgical data were available for 453 (90%) patients. The median time to surgery in Regimen-C was 52 days (95% CI = 49 to 54), and in Regimen-DI it was 56 days (95% CI = 55 to 57), HR = 0.89, $P = .20$ (Fig. 3, B). Limb salvage was the most common operation and was performed in 164 (74%) and 170 (73%) patients in Regimen-C and regimen-DI, respectively. Of patients who had surgery, 84% underwent the planned operation. There was no evidence of a difference in immediate or late postoperative complication rates according to treatment regimen.

Histologic Response

Histologic diagnosis was confirmed in 461 (93%) patients, and histologic subtype was assessable in 441 (89%) patients of the 497 patients eligible (Table 1). Resected tumor specimens were reviewed in 403 (89%) of the 453 trial patients with surgical details. Good response was observed in 71 (36%) of the assessable Regimen-C patients and 103 (50%) Regimen-DI patients (RR = 1.30; 95% CI = 1.09 to 1.54; $\chi^2_1 = 9.01$, $P = .003$). Median time to surgery was 56 days in the 229 (57%) good responders and 53 days in the 174 (43%) poor responders (HR = 1.26, $P = .023$).

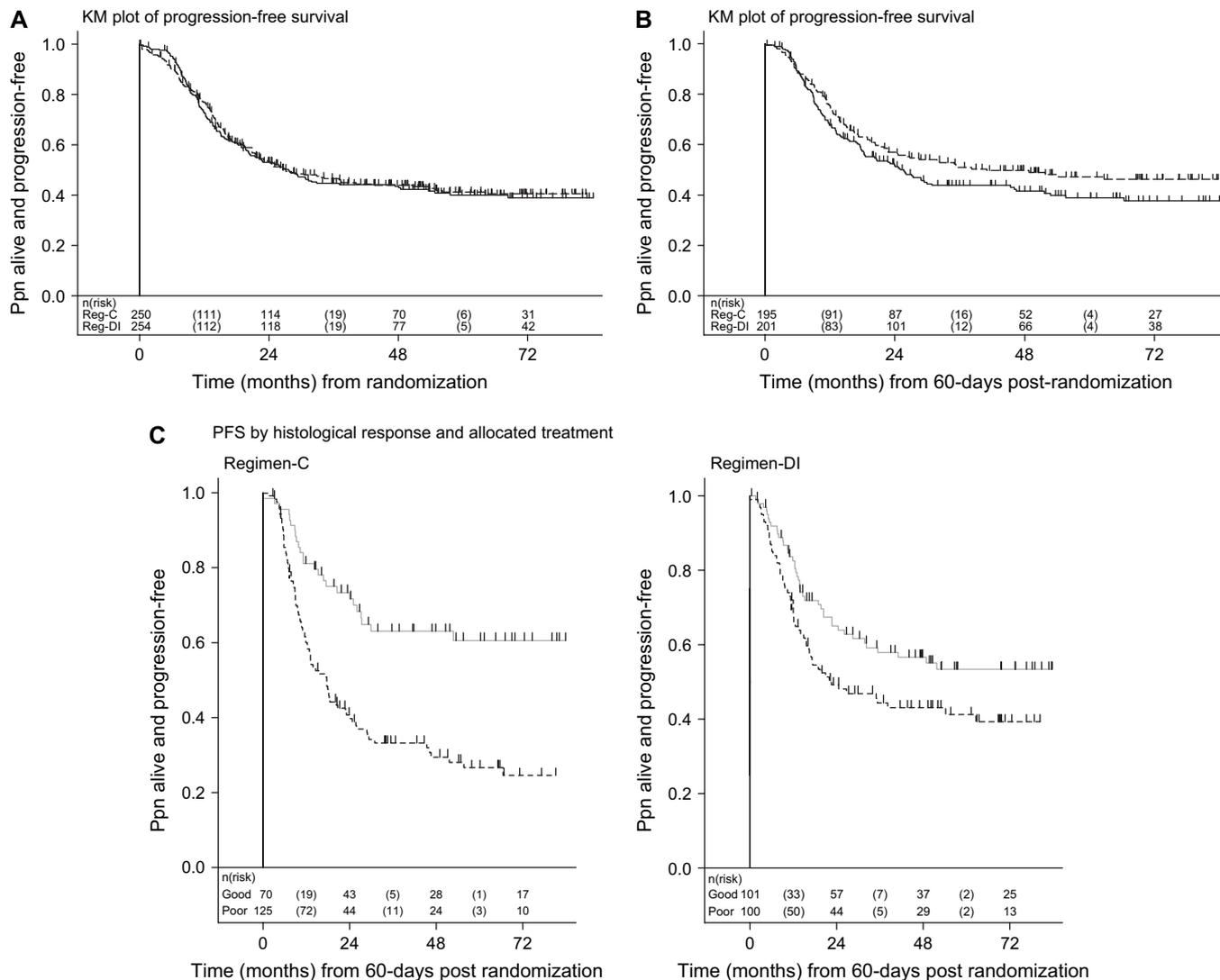


Fig. 5. Progression-free survival according to allocated treatment. Progression-free survival (PFS) for patients treated with conventional regimen (Regimen-C [solid line]) and dose-intensive regimen (Regimen-DI [dashed line]) was calculated from the time of randomization (hazard ratio [HR] = 0.98, 95% confidence interval [CI] = 0.77 to 1.24) (A) or from 60 days after randomization (HR = 0.82, 95% CI = 0.63 to 1.08) (B) when

histologic response was known. C) Progression-free survival for patients allocated to Regimen-C (left panel) or Regimen-DI (right panel) according to histologic response (good [solid line] or poor [dashed line]). Hatch marks denote censoring events. Numbers at risk are shown below each graph.

The proportions of Regimen-C and Regimen-DI patients with a good response after two preoperative cycles were 26% (95% CI = 20% to 34%) and 14% (95% CI = 3% to 36%). The proportions of patients with a good response after three preoperative cycles were 40% (95% CI = 26% to 56%) and 45% (95% CI = 38% to 52%) on Regimen-C and Regimen-DI, respectively. Among the 11 Regimen-C and the 20 Regimen-DI patients who received four preoperative cycles, the proportion with a good response was 64% (95% CI = 31% to 89%) and 65% (95% CI = 41% to 85%). Thus, the proportion of patients with observed good histologic response increased with the number of preoperative cycles.

Clinical Outcome Measures

Progression-free survival. Kaplan–Meier estimates of progression-free survival according to the received treatment were derived (Fig. 5, A). The estimated 5-year progression-free survival rates were 39% (95% CI = 33% to 46%) for Regimen-C and 41% (95%

CI = 34% to 47%) for Regimen-DI (HR = 0.98, 95% CI = 0.77 to 1.24). There was no evidence of a statistically significant difference in progression-free survival between treatment regimens based on the log-rank test ($\chi^2 = 0.05, P = .83$).

In landmark analyses timed from 60 days after randomization and including 395 patients, the hazard ratio for progression-free survival was 0.82 (95% CI = 0.63 to 1.08; log-rank $\chi^2 = 2.06, P = .15$) in favor of Regimen-DI (Fig. 5, B). Stratifying for histologic response (good or poor), the landmark analysis hazard ratio for progression-free survival was 0.88 (95% CI = 0.67 to 1.16; log-rank $\chi^2 = 0.84, P = .36$) in favor of Regimen-DI. Using the landmark time and patient group in a Cox model including allocated treatment, histologic response, and an interaction term for allocated treatment and histologic response, allocated treatment was not a statistically significant determinant of outcome (HR = 1.23, 95% CI = 0.75 to 2.02) whereas histologic response was prognostic (HR = 2.64, 95% CI = 1.69 to 4.12). There was no good evidence of interaction

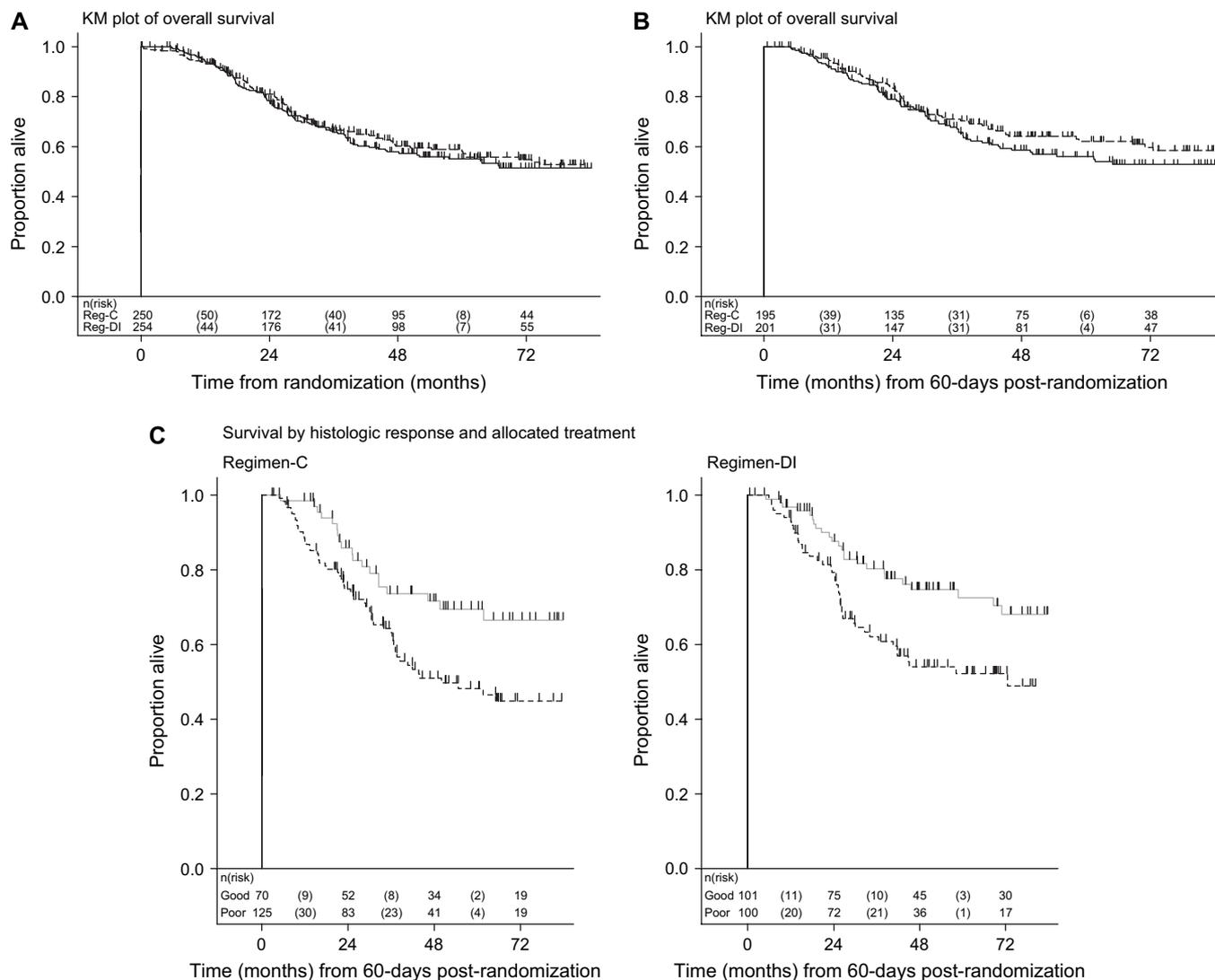


Fig. 6. Overall survival according to allocated treatment. Survival for patients treated with conventional regimen (Regimen-C [solid line]) and dose-intensive regimen (Regimen-DI [dashed line]) was calculated from the time of randomization (hazard ratio (HR) = 0.94, 95% confidence interval [CI] = 0.71 to 1.24) (A) or from 60 days after randomiza-

tion (HR = 0.83, 95% CI = 0.60 to 1.15) (B) when histologic response was known. C Overall survival for patients allocated to Regimen-C (left panel) or Regimen-DI (right panel) according to histologic response (good [solid line] or poor [dashed line]). Hatch marks denote censoring events. Numbers at risk are shown below each graph.

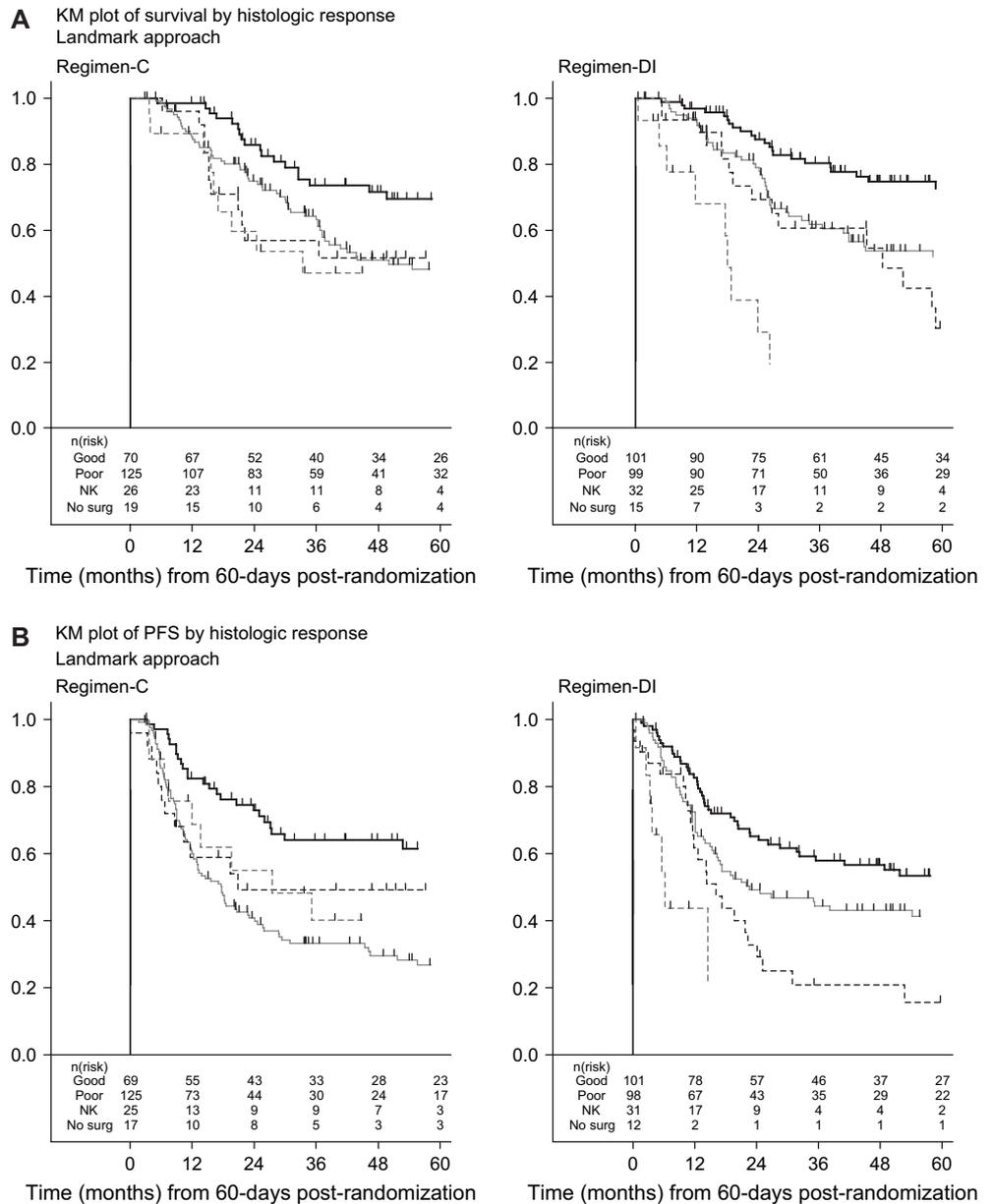
between these factors ($P = .10$). Reported progression at any time on Regimen-C and Regimen-DI, respectively, were as follows: local progression 22 (9%) versus 11 (4%), local recurrence 44 (18%) versus 23 (9%), and distant metastases 107 (44%) versus 113 (45%). Regardless of allocated treatment, patients with good histologic response had improved progression-free survival in landmark analyses (compared with patients with poor response, HR = 0.50, 95% CI = 0.38 to 0.66, $\chi^2 = 23.30$, $P < .001$), with 3-year and 5-year progression-free survival rates of 60% and 56%, respectively, in good-response patients and 38% and 33%, respectively, in poor response patients.

Overall Survival. At the time of analysis (February 2005), 193 deaths had been reported (98 in Regimen-C and 95 in Regimen-DI). The reported causes of deaths were similar according to allocated treatment with the deaths of 93 patients (95%) on Regimen-C and 88 patients (93%) on Regimen-DI attributed to osteosarcoma.

The other 12 deaths were attributed to treatment, although treatment-related deaths occurred during the protocol treatment period for only three patients, all on Regimen-DI. The hazard ratio for overall survival was 0.94 (95% CI = 0.71 to 1.24) with no evidence of a difference between treatment regimens based on Kaplan–Meier estimates (Fig. 6, A; log-rank $\chi^2 = 0.22$, $P = .64$). The 5-year overall survival rates were 55% (95% CI = 48% to 62%) for Regimen-C and 58% (95% CI = 51% to 65%) for Regimen-DI.

In landmark analyses, 145 of the 395 patients eligible for these analyses had died (HR = 0.83, 95% CI = 0.60 to 1.15; log-rank $\chi^2 = 1.24$, $P = .26$) in favor of Regimen-DI (Fig. 6, B). Kaplan–Meier estimates for progression-free survival on both regimens in which patients are stratified by histologic response were derived (Fig. 6, C). Stratifying for good and poor histologic response, the landmark analysis hazard ratio for survival was 0.91 (95% CI = 0.66 to 1.26; log-rank $\chi^2 = 0.31$, $P = .58$) in favor of Regimen-DI. In a Cox model that included allocated treatment, histologic response, and an

Fig. 7. Overall and progression-free survival (PFS) according to histologic response and whether surgery was performed. Overall survival (A) and progression-free survival (B) were calculated from 60 days after randomization for patients on the conventional regimen (Regimen-C, left panels) or the dose-intensive regimen (Regimen-DI, right panels) according to histologic response (good [solid black lines], poor [solid gray lines], or unknown [NK; dashed black lines] and in cases where surgery was not performed [No surg; gray dashed lines]). Numbers at risk are shown below each graph.



interaction term for these variables, treatment was not statistically important (HR = 0.89, 95% CI = 0.49 to 1.62) and histologic response was important (HR = 2.01, 95% CI = 1.20 to 3.38), and there was no evidence of interaction between these factors ($P = .92$). Regardless of allocated treatment, patients with good histologic response had improved survival over patients with poor histologic response (HR = 0.50, 95% CI = 0.36 to 0.70, $\chi^2 = 15.52$, $P = .0001$); the 3-year and 5-year survival rates were 78% and 71%, respectively, in good-response patients and 63% and 49%, respectively, in patients with poor response.

In exploratory landmark analyses using the 487 patients who were alive 60 days after randomization, by which time surgery should have been performed, those patients who had surgery but for whom histologic response was not available had poorer survival than both good-response patients (HR = 2.61, 95% CI = 1.53 to 2.75) and poor-response patients (HR = 1.29, 95% CI = 0.76 to 2.20). Patients for whom no surgery was reported had even worse

survival compared with good responders (HR = 4.05, 95% CI = 1.97 to 8.31) (Fig. 7, A). A similar trend was noted for progression-free survival (Fig. 7, B).

A series of univariate and multivariate Cox regression models based on chemotherapy and outcome data from 485 patients who received chemotherapy (one patient with a large overdose was excluded) showed no good evidence that received cisplatin dose, cisplatin dose intensity, doxorubicin dose, or doxorubicin dose intensity (whether preoperative or overall) affected overall survival. There was a suggestion that increased preoperative and overall cisplatin dose may be associated with improved survival: each 10% increase in preoperative standardized cisplatin dose was associated with an improvement in survival (HR = 0.87, 95% CI = 0.76 to 0.99) as was each 10% increase in overall standardized cisplatin dose (HR = 0.88, 95% CI = 0.77 to 1.00).

Sensitivity analyses were performed to assess the impact of the modified intention-to-treat approach by examining the results

of all 504 randomly assigned patients. The hazard ratios for progression-free survival and overall survival in this total population were the same as for the modified intention-to-treat population ($n = 497$) that was analyzed.

Discussion

Here, we have presented results for the third EOI randomized controlled trial in osteosarcoma. This trial was designed to prospectively test the hypothesis that increasing the planned dose intensity of the EOI cisplatin and doxorubicin regimen by a factor of 1.5 would improve outcome for patients with nonmetastatic limb osteosarcoma. The trial involved 48 centers in 11 countries. In this complex setting, we have demonstrated that patients randomly assigned to the dose-intensive arm, Regimen-DI, received treatment at increased dose intensity compared to patients in the conventional arm, Regimen-C. Despite the relatively large number of patients, 5-year median follow-up, and more events reported than were planned, the trial was only powered to detect a relatively large 15% absolute difference (HR = 0.6) between arms. Consequently, the trial had limited power to detect a smaller but still clinically relevant benefit of Regimen-DI. With this data an absolute difference in overall survival of 10% cannot be excluded.

Perhaps not surprisingly, patients receiving G-CSF in Regimen-DI had substantially less grade 3–4 neutropenia but statistically significantly increased thrombocytopenia compared with patients in Regimen-C. Hematologic toxicity was the main reason for delays and dose reductions. There were concerns that a dose-dense schedule might lead to increases in other acute toxicities, but there was no good evidence from this trial to support this possibility, except for increases in mucositis and ototoxicity that were of borderline statistical significance. There were also particular concerns before the trial that doxorubicin every 2 weeks might provoke increased early cardiotoxicity, but there was no consistent evidence of this (data not shown).

Overall in this trial, patients receiving Regimen-DI received their total treatment at 31% greater intensity relative to those receiving Regimen-C—less than the planned 50% increase. As expected from clinical experience, the actual intensity of both arms was less than planned. In fact, the observed intensity for Regimen-DI was close to, but more than, the planned intensity for Regimen-C. Although patients in both arms experienced delays and dose reductions, patients allocated to Regimen-C were more likely to have their chemotherapy doses reduced because of toxicity. They were also more likely than those on Regimen-DI to receive treatment on time. Patients allocated Regimen-DI had close to full-dose treatment, but with substantially increased delays. There was no evidence that dose intensity varied systematically according to disease or patient characteristics.

Histologic response to chemotherapy has repeatedly been demonstrated to be a major prognostic indicator in osteosarcoma and is sometimes used as a surrogate marker of outcome (3235). This study confirmed that patients with good response (>90% tumor necrosis) had outcomes that were improved to a statistically significant extent compared to those with poor response ($\geq 10\%$ viable cells), with reported 5-year survival of rates 71% and 51%, respectively. This trial also demonstrated a statistically significant

increase in the rate of good histologic response for Regimen-DI over that of Regimen-C (50% versus 36%). However, this advantage in histologic response did not translate into a demonstrable survival benefit. This suggests that histologic response would not be a good surrogate measure despite previous indications, and this observation demands further exploration.

One possible explanation for the fact that histologic response was not associated with overall survival is that the association was obscured by the results of patients whose histologic response was not assessed. In this trial, patients with unknown histologic response had worse outcomes than would have been predicted for a randomly selected representative group of trial patients (Fig. 7). However, the landmark analyses accounted for this by including only patients for whom both surgery and histologic response data were available.

Most Regimen-DI patients received three cycles of preoperative chemotherapy, one cycle more than that received by most Regimen-C patients, and they received a 50% greater preoperative chemotherapy dose. This raises the possibility that histologic response might be dependent on dose per se, rather than on dose intensity. There is support for this hypothesis because exploratory analyses showed similar increases in histologic response rates in both arms according to the number of preoperative cycles. Although the proportion of histologic responders increased with increased standardized preoperative dose, the proportion of responders did not show a clear increase with increasing standardized dose intensity. These observed trends are not based on a randomized comparison and therefore should be treated with caution.

The favorable histologic response rate (50%) for Regimen-DI in this trial is higher than that seen with cisplatin and doxorubicin in previous trials (response rates 30%–35%) (6,7), even though preoperative doses were the same and planned time to surgery was shorter (6 versus 9 weeks). Thus, either increasing dose intensity has led to increased tumor necrosis or the technical assessment of histologic response has changed over time so that increased numbers of tumors are deemed to have responded. The latter possibility seems unlikely given that the methodology was the same as that used in previous EOI trials (with several of the same reference pathologists analyzing the data) (43) and the fact that changes in assessment should have affected both trial arms. An alternative explanation for the observed increase in favorable histologic response in Regimen-DI is that more intensive chemotherapy delivery alters sensitivity and specificity of the histologic response assessment so that despite the appearance of good histologic response, greater numbers of cells survive. Progression-free survival for patients with good histologic response was slightly less in Regimen-DI than in Regimen-C and for poor responders slightly better (Fig. 5, C), suggesting that the interpretation of good response may be different for patients receiving the dose-intensive schedule. Certainly, these results challenge the emphasis placed on histologic response as the key treatment-related prognostic factor (20,45) and suggest that the predictive value of histologic response may be protocol specific. Although inappropriate as a surrogate outcome measure, pathological response to preoperative chemotherapy is able to select for patients with good prognosis.

With the completion of this trial, the EOI has carried out three randomized controlled trials since 1983, all incorporating a

control arm planned to deliver six cycles of cisplatin and doxorubicin every 3 weeks with surgery after two or three cycles. None of the research arms (three drug, multidrug, or dose intensified) have demonstrated any statistically significant benefit over this conventional arm. In this trial, the 5-year progression-free survival and overall survival for nonmetastatic high-grade limb osteosarcoma in the conventional arm were 39% and 55%, respectively. These percentages do not compare favorably with outcomes reported by other large cooperative groups. Cooperative Osteosarkomstudiengruppe (COSS) reported 10-year progression-free survival of 49% and overall survival of 60% in 1702 patients entered into all their studies. The COSS trial encompassed several randomized controlled trials and included patients with axial primaries and metastases (46). The Children's Oncology Group (COG), after conducting the largest multi-institutional randomized controlled trial in osteosarcoma and using the three-drug regimen of cisplatin, doxorubicin, and high-dose methotrexate, reported 3-year progression-free survival and overall survivals of 71% and 80%, respectively (11). Results of broadly similar magnitude have been reported by other multi-institutional groups although not in randomized controlled trials (45,47). Comparisons across trials and between groups are complex and unreliable, but it is difficult not to conclude there might be identifiable factors accounting for the results from the EOI trials. One difference is that other groups have, in general, used longer regimens with more drugs.

This EOI trial recruited 504 patients over a period of 9 years and is the second largest osteosarcoma randomized controlled trial. Although this is a relatively large randomized controlled trial in the field of osteosarcoma, it clearly has its limitations because of the trial size. EOI has recently joined with other large trials groups (COG, COSS, and Scandinavian Sarcoma Group) to form EURAMOS: the EUROpean and AMerican OsteoSArcoma group. This is an international intergroup aiming to develop and conduct randomized controlled trials pertaining to osteosarcoma and associated studies. EURAMOS plans to recruit more than 400 patients per year, and the first EURAMOS randomized controlled trial, EURAMOS 1, opened to recruitment in 2005 (48). EURAMOS 1 is using pathologic response to stratify patients by risk and then perform separate randomizations for good-response and poor-response patients; the standard arm in each group uses a three-drug regimen of cisplatin, doxorubicin, and high-dose methotrexate; good responders are randomly assigned to continue standard treatment and follow this with maintenance therapy with pegylated interferon; poor responders are randomly assigned to supplement the cisplatin, doxorubicin, and high-dose methotrexate with ifosfamide and etoposide.

Our trial had a number of limitations and compromises. We had to make a pragmatic decision about the timing of surgery, and there were positives and negatives to each of the approaches: either choice could have affected the surrogate outcome of histologic response to preoperative treatment. The negative is that patients did not have a fixed dose of chemotherapy before surgery, but we felt this was outweighed by the positives of ensuring that surgery, the primary therapy for these patients, was at a fixed time on each arm and that histologic response was assessed at the same point in time. The trial took a long time to recruit and mature. Largely, this is because of the rarity of the condition. This has led to the decision

to participate with other cooperative groups in future trials. The multicountry nature of the trial added some difficulties, especially where countries vary in their standard approaches to chemotherapy and surgery. In this context, central pathology review was not complete in all cases and data collection was difficult to organize. With the main participating countries, these were not problematic, but data collection and histologic response were more difficult to organize in certain countries which had communication difficulties.

In summary, this was one of the largest trials in osteosarcoma, and it tested the use of dose-intensified perioperative chemotherapy. Both regimens planned the same total chemotherapy doses and both planned surgery at day 42. Most patients experienced some form of grade 3 or 4 toxicity. Regimen-DI resulted in more tumors having good histologic response to preoperative chemotherapy, but this did not translate into a demonstrable patient benefit in overall survival or progression-free survival over Regimen-C. The emphasis placed on histologic response as the key treatment-related predictive factor is thereby challenged (20). Clinical outcomes measures for this patient group need to be further improved.

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Appendix

The EOI was formed in 1982 to facilitate sufficiently sized randomized controlled trials. It has had representation from National Cancer Research Institute Sarcoma Clinical Studies Group, U.K. Children's Cancer Study Group, Société Internationale d'Oncologie Paediatrice (SIOP), and EORTC Soft Tissue and Bone Sarcoma Group.

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MRC Participating Centers (country: number of patients—hospital, oncologists)

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EORTC Participating Centers (country: number of patients—hospital, oncologists)

The Netherlands (78): Leiden University Hospital (40; M. Nooij); UMC Nijmegen (20; J. Bokkerink); Amsterdam, Emma Kinderziekenhuis (12; H. van den Berg); Amsterdam, Onze Lieve Vrouw Gasthuis (5; K. Rozendaal); Utrecht UMC Academisch Ziekenhuis (1; A. de Graeff); **Saudi Arabia (52):** Riyadh, King Faisal Specialist Hospital and Research Centre (52; M. Memon); **Belgium (38):** Leuven, U. Z. Gasthuisberg (14; A. T. Van Oosterom, A. Uyttebroeck); Brussels, Cliniques Universitaires St Luc (11; B. Brichard, A. Zenebergh); Universitair Ziekenhuis Antwerpen (8; J. B. Vermorken); Brussels Institut Jules Bordet (5; A.

Awada, T. H. Gil); **Denmark (25):** Aarhus Kommunehospital (23; O. S. Nielsen); Copenhagen, Rigshospitalet (2; C. Rechnitzer); **South Africa (6):** Pretoria Academic Hospital University (6; L. de Jager); **Greece (5):** Athens, Aghia Sophia Children's Hospital (5; S. Polychronopoulou); **Portugal (5):** Instituto Portugues de Oncologia de Francisco Gentil—Centro De Lisboa (5; A. Fernandes); **France (2):** Rennes, Centre Eugene Marquis (2; P. Kerbrat); **Slovenia (1):** The Institute of Oncology (1; B. Zakotnic).

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Notes

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