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Adjuvant and neoadjuvant chemotherapy for osteosarcoma of the extremities: 27 year experience at Rizzoli Institute, Italy

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Abstract

Around 1148 patients with non-metastatic osteosarcoma of the extremity were treated in a single institution between 1972 and 1999 with 4 different protocol of adjuvant and 7 different protocols of neoadjuvant chemotherapy. The rate of limb salvage increased from 20% to 71%. The 5-year event-free survival (EFS) and overall survival (OS) were 57% and 66%, respectively. The 10-year EFS and OS were 52% and 57%, respectively, and the results significantly correlated with serum alkaline phosphatase levels; the type of chemotherapy (adjuvant *vs* neoadjuvant); and with histologic response to pre-operative treatment. Aggressive chemotherapy and surgery could cure about the 60% of patients with osteosarcoma of the extremity. However, since local or systemic relapses, myocardiopathies and a second malignancy are possible even 5 or more years since the beginning of treatment, a long-term follow-up is recommended.

Keywords: Osteosarcoma; Chemotherapy; Follow-up

1. Introduction

Adjuvant and neoadjuvant chemotherapy, introduced in the early 1970s, have significantly improved the long-term survival rate for patients with high-grade osteosarcoma of the extremities. The 5-year disease-free survival has in fact improved from less than 20% to more than 60%. Simultaneously, the frequency of limb salvage surgery increased from 10–20% to 80–90%, with a corresponding decrease in the amputation rate. Many of the larger series of adjuvant and neoadjuvant treatments for osteosarcoma reported in the literature have two main defects: (a) in many of these series, the results are reported in terms of probability of event-free survival up to 5 years that have been calculated from studies where minimum follow-up was often less than three years. And only few studies update their results; (b) in most studies little is known about the post-relapse treatments and outcome of patients who develop metastases and/or local recurrence; and (c) practically none of the studies have reported in detail the surgical treatment, margins and complications.

In this paper, we report the long-term results (1972–1999) achieved in a large series of patients in a single institution. Patients (1148) with non-metastatic osteosarcoma of the extremity were treated with adjuvant and neoadjuvant chemotherapy. Patients who developed local recurrence and/or systemic relapse; the post-relapse

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treatments; and outcome are also reported. In addition, surgical details and arising complications have also been evaluated.

2. Patients and methods

2.1. Patient selection and pathology

Patients were considered eligible for the trial when they fulfilled the following criteria: typical radiographic and histologic features of primary, high-grade, central osteosarcoma; tumour located in the extremity; no previous history of cancer and no prior treatments; age under 40; no associated disease contraindicating chemotherapy; and no evidence of metastases at diagnosis.

Of the 1759 newly diagnosed cases of osteosarcoma observed at Istituto Ortopedico Rizzoli, Bologna, Italy between March 1972 and June 1999, 1348 patients (77%) were eligible for the study. All the eligible patients were offered, according to the period of observation, an adjuvant or neoadjuvant treatment after having been informed of the potential advantages and risks. Of the 1348 eligible patients, 200 declined entry into the study.

Table 1
Patients' features and 5-year event-free survival

Features	Total patients	5-year event-free survival (%)	*P*
Gender			
Male	670 (58%)	55	0.005
Female	478 (42%)	59	
Age			
<14 years	460 (40%)	55	0.45
⩾14 years	688 (60%)	58	
Site			
Femur	612 (53%)	56	0.76
Tibia	327 (28%)	57	
Humerus	128 (11%)	61	
Fibula	60 (7%)	48	
Other bones	21 (1.8%)	67	
Histology			
Osteoblastic	601 (64%)	56	0.0001
Chondroblastic	92 (10%)	57	
Fibroblastic	84 (9%)	75	
Telangiectatic	68 (7%)	76	
Small cells	5 (0.4%)	40	
Not classifiable	81 (9%)	73	
Data missing	217 (19%)	41	
SALP			
Normal	704 (61%)	67	0.0001
Elevated	444 (39%)	41	
Tumour volume			
<150 ml	395 (48%)	65	0.08
⩾150 ml	430 (52%)	57	
Pathologic fracture			
Yes	88 (8%)	54	0.43
No	1060 (92%)	57	

The remaining 1148 patients are the focus of this article and their characteristics are presented in Table 1.

The diagnosis of osteosarcoma, established by clinical and radiological findings, was always confirmed on histologic slides of tumour tissue obtained from an open or needle biopsy as well as from resected specimen. Tumours were classified as conventional, telangiectatic, or small-cell osteosarcoma. On the basis of the predominant intercellular material, conventional osteosarcoma was classified as osteoblastic, fibroblastic or chondroblastic subtype. The subtype distinction was made from surgical specimens, and was possible in all but 81 cases, which were defined as "not classifiable". In 217 cases, histotype data was missing.

2.2. Pre-operative evaluation

A complete history was taken from all patients including a thorough physical examination and several chemical laboratory tests. The primary tumour was evaluated on standard radiographs, Technetium 99-MDP bone scans. CT scans were used only in the 1012 patients treated after 1980. MRI was performed in approximately half the patients. These investigations were repeated before surgery. Bone metastases were investigated with total body scans, whereas standard chest radiographs and lung CT scans were used to exclude lung metastases for 1012 patients treated after 1980 and by full chest tomography for136 patients treated before 1980.

2.3. Chemotherapy

Patients were treated with 11 different protocol of chemotherapy: 4 adjuvant (Table 2) and 7 neoadjuvant (Table 3). These protocols have been reported in detail in elsewhere [1–5].

2.4. Surgery and pathological evaluation

The type of surgery (amputation, rotationplasty or limb salvage), as well as the type of reconstruction after resection (prosthesis; Kunstscher rod or plate and cement; vascularised fibula combined with allograft;

Table 2
Protocols of adjuvant chemotherapy

Protocol	Period	Number of patients	Drugs
IOR/OS-A1	1972–1974	55	VC–ADM–*LD*MTX
IOR/OS-A2	1975	35	ADM
IOR/OS-A3	1976–1978	42	VC–MTX (moderate doses)–ADM
IOR/OS-A4	1979–1981	116	VC–MTX–ADM *vs* VC–*HD*MTX–ADM

V = Vincristine; C = Cyclophosphamide; ADM = Doxorubicin; MTX = Methotrexate (*LD* = low doses, *HD* = high doses).

Table 3
Protocols of neoadjuvant chemotherapy

Protocol	Period	Number of patients	Preoperative treatment	Postoperative treatment
IOR/OS-N1	1983–1986	127	*HD*MTX–CDP *vs* MTX–CDP	Good responders: MTX–CDP–ADM Poor responders: ADM–BCD
IOR/OS-N2	1986–1989	165	MTX–CDP–ADM	Good responders: MTX–CDP–ADM Poor responders: MTX–CDP–ADM–IFO–ETO
IOR/OS-N3	1990–1993	156	MTX–CDP–*LD*ADM	Good responders: MTX–CDP–*LD*ADM Poor responders: MTX–CDP–*LD*ADM–IFO–ETO
IOR/OS-N4	1994–1995	132	*HD*MTX–CDP–ADM–IFO	Good & poor responders: *HD*MTX–CDP–ADM–IFO
IOR/OS-N5	1996	68	*HD*MTX–CDP–ADM–*HD*IFO	Good responders: *HD*MTX–CDP–ADM–*HD*IFO (3 cycles) Poor responders: *HD*MTX–CDP–ADM–*HD*IFO (4 cycles)
IOR/OS-N6	1997	128	As protocol IOR/OS-N5	As protocol IOR/OS-N5
IOR/OS-N7	1998–1999	124	As protocol IOR/OS-N2 *vs* As protocol IOR/OS-N4	As protocol IOR/OS-N2 *vs* As protocol IOR/OS-N4

MTX = Methotrexate (*LD* = low doses, *HD* = high doses). CDP = Cisplatin. ADM = Doxorubicin (*LD* = low doses, *HD* = high doses). BCD = Bleomycin + Cyclophosphamide + Dactinomycin. IFO = Ifosfamide (*LD* = low doses, *HD* = high doses). ETO = Etoposide.

allograft and autograft) were chosen depending on the location and extension of the tumour; neurovascular structure involvement; skeletal maturity; desired life-style; and presence of complicating factors, such as displaced pathologic fractures or infected biopsy sites. For conservative surgery, during the 28-year span of the study, it was always considered mandatory that the pre-operative staging assured the possibility of achieving wide surgical margins and preserving a limb that could at least be partially functional after reconstruction. After surgery, the surgeons and the pathologists reviewed the gross specimens to determine surgical margins following Enneking's classification [6]. The margins were "adequate" if radical or wide, and "inadequate" if margins were marginal, intralesional, or contaminated.

In patients treated with neoadjuvant chemotherapy, the histologic response to chemotherapy was evaluated following the criteria previously reported [7] and graded as "good" (90% or more tumour necrosis) or "poor" (less than 90% tumour necrosis). These two grades roughly correspond to grades III and IV and to grades I and II of the descriptive classification proposed by Rosen et al. [8].

2.5. Follow-up

During post-operative chemotherapy, besides clinical evaluation, patients were checked every two months with radiographs or CT scan of the chest and of the operated limb. Additional investigations were performed only if there was a clinical and/or radiographic suspicion of relapse. After completion of chemotherapy, patients were followed in the outpatient clinic with radiographs or CT every 2 months for two years, every 3 months in the third year and then every 6 months. After the fifth year, patients were checked annually with radiographs of the involved bone and chest, up to the tenth year. All patients were followed for at least 5 years after treatment unless they relapsed or died.

2.6. Statistics

The major aim of the study was the event-free survival (EFS) evaluation; recurrence, death from toxicity; and second malignancy were all considered adverse events. Overall survival (OS) was also evaluated, but these data should be considered with caution. When recurrent disease occurred, the post-relapse treatment offered was not homogeneous and changed radically during the 28 years of the study period. EFS was calculated from the first day of pre-operative chemotherapy to the first adverse event or to the most recent follow-up examination; OS was calculated from the first day of chemotherapy until death or last follow-up. The survival curves were calculated according to the Kaplan–Meier method and compared by means of the long-rank test. The Cox proportional hazards regression analyses and Wald test was used for multivariate analyses to test predictive factors for survival. The frequency of distribution of different parameters was compared among groups of patients by means of the Chi-square test. Significance was set at $P < 0.05$.

3. Results

3.1. Recruitment and distribution of demographic and tumour related variables

The median number of patients who entered into the 10 trials were 43 for each year and ranged from 14 cases in 1972 to 60 cases in 1999. There were 670 male (58%) and 478 female (42%). The median age at diagnosis was 16.7 year (3–40); 17.1 for male and 16.1 for female.

Cases in toddlers were rare, with only 21 patients (2%) presenting in the first 5 years of life. Around 157 patients (14%) were in the first decade of life, 775 (68%) in the second, 143 (12%) in the third and 73 (6%) in the fourth. Around 1003 tumours were located in the legs (87%) and 145 (13%) in arms. The distribution in single bones were: femur 612 cases (53%), tibia 327 (28%), humerus 128 (11%), fibula 60 (5%) and others 21 (2%). From the available tumours in 642 cases, the median volume was 225 ml (10–4393). The median volume was 270 ml for tumours located in the femur; 202 ml for tumours located in the tibia; and 181 ml for tumours located in the humerus and these difference were statistically significant ($P < 0.001$). In 490 (76%) patients the tumour volume was less than 300 ml and in 152 (24%) more than 300 ml. Eighty-eight patients had pathologic fracture at the time of diagnosis (8%). The alkaline phosphatase levels were elevated in 444 (39%) patients and normal in 704 (61%). Among patients with elevated alkaline phosphatase levels, 105 had enzyme values that were more than 4 times the normal. The histologic subtypes available are reported in Table 1.

3.2. Surgery and surgical margins

Around 817 (71%) patients were treated with limb salvage, 289 (26%) with amputation and 38 (3%) with rotationplasty. Four patients were not operated; two died of toxicity during pre-operative treatment; another developed unresectable lung metastases before surgery and was locally treated with radiotherapy; and the last patient committed suicide before surgery. The rate of amputation was significantly different according to the period in which the trials were performed. For instance, this rate was 80% for the 248 patients treated with adjuvant chemotherapy from 1972 to 1982 and 10% for the 900 patients treated with neoadjuvant chemotherapy from 1983 to 1999. In latter group of patients, the rate of amputation between 1983 and 1986 was 25% for the 127 patients treated with the first neoadjuvant protocol (IOR/OS-N1); and 4% for the 124 treated between 1998 and 1999 with the neoadjuvant protocol (IOR/OS-N5). In limb salvage procedures, reconstruction was prosthesis in 524 (64%) of patients; Kuntscher rod or plate plus cement in 34 (4%); vascularised fibula combined with graft in 50 (6%); allograft in 84 (10%); and autograft in 65 (8%). No reconstruction was necessary in 60 patients (7%) with tumours located in the fibula.

The surgical margins were radical in 125 (11%) patients all treated by amputation; wide in 913 (79%); marginal in 75 (7%); and intralesional or contaminated in 31 (3%). According to the type of surgery, the surgical margins were inadequate (marginal or intralesional) in 15 of the 289 amputated patients (5%); in 81 of the 817 limb salvages (10%); and in 4 among the 38 rotationplasty (10%). These differences were highly significant ($P < 0.0001$).

According to the type of chemotherapy, the rate of inadequate surgical margins was 11% in the 248 patients treated with adjuvant chemotherapy and 8% in the 896 patients treated with neoadjuvant chemotherapy ($P < 0.09$). It must be remembered that in most cases treated with adjuvant chemotherapy the pre-operative staging was made only on radiographs and not with computed tomography (CT) or Magnetic Resonance Imaging (MRI).

3.3. Histologic response to pre-operative treatment in patients treated with neoadjuvant chemotherapy

In patients who received neoadjuvant treatment, chemotherapy-related tumour necrosis was good in 556 (62%) and poor in 340 (38%). The rate of good histologic responses was not related to patients, age, site or size of tumour, or serum alkaline phosphatase levels at presentation. The rate of good histologic response was slightly better for female than for male (65% *vs* 59%, $P < 0.05$). According to the histologic subtype, the 88 patients with chondroblastic tumours showed a significantly lower percentage of good responses compared to other subtypes (50% *vs* 63% $P < 0.01$); while the 62 telangiectatic osteosarcoma had a significant higher rate of good histologic response (87% *vs* 60%, $P < 0.0001$).

3.4. Event-free survival

At a median follow-up of 5–27 years (median 14.8), 635 patients (55.3%) remained continuously event-free; 488 relapsed (42.5%); 18 died from toxicity; and 7 died due reasons not related to osteosarcoma or chemotherapeutic treatment (2 suicide, 2 pulmonary embolism, 1 complication of CVC, 1 car crash and 1 second malignancy). The 5-year event-free survival (EFS) was 57% and the overall survival 66%. Since all patients were followed for at least 5 years after treatment, EFS value is a true reflection of treatment outcome. The median dose-intensity [4] of patients who remained continuously free of disease was essentially the same as the median dose of patients who relapsed (88.7% *vs* 87.9%). As shown in Table 1, by univariate analysis, the 5-year EFS rate was higher for female than for males (59% *vs* 55%, $P < 0.09$); for fibroblastic conventional osteosarcoma than for chondroblastic and osteoblastic subtypes (82% *vs* 55%, $P < 0.0001$); and for patients with normal serum values of alkaline phosphatase than for patients with high-level (67% *vs* 41%, $P > 0.0001$). Alkaline phosphatase levels were not only a significant prognostic factor, but there was also a correlation between increased alkaline phosphatase value and prognosis. In fact, the 5-year EFS was 24% for patients with serum alkaline phosphatase levels more

Table 4
5-year event-free survival according to different variables

Variables	Total pts	5-year EFS[a] (%)	*P*
Surgery			
Amputation	289 (26%)	53	<0.001
Limb salvage	817 (71%)	61	
Rotation plasty	38 (3%)	58	
Surgical margins[b]			
Adequate	1044 (91%)	58	<0.03
Inadequate	100 (9%)	46	
Histologic response			
Good	556 (62%)	67	<0.0001
Poor	340 (38%)	48	
Type of chemotherapy			
Adjuvant	248 (22%)	43	<0.0001
Neoadjuvant	900 (78%)	61	

[a] Patients who died of reasons unrelated to disease were not considered.
[b] 4 patients did not undergo surgery.

Table 5
Multivariate analysis for prognostic factors in patients with non-metastatic osteosarcoma of the extremities treated according adjuvant and neoadjuvant chemotherapy protocols

Variable	Relative risk	95% CI	Wald test
SALP			
Normal	1		
Elevated	2.31	1.86–2.87	$P < 0.0005$
Type of chemotherapy			
Neoadjuvant	1		
Adjuvant	1.66	1.36–2.04	$P < 0.0005$
Histologic response to chemotherapy			
Good	1		
Poor	1.87	1.50–2.32	$P < 0.0005$
Tumour volume			
<150 ml	1		
⩾150 ml	1.26	1.01–1.57	$P < 0.04$

than 4 times higher than normal and 46% for patients with high values below this limit ($P < 0.001$). As illustrated in Table 4, the 5-year EFS according to treatment variables was significantly higher in patients treated with limb salvage than in patients treated with amputation or rotationplasty (61% *vs* 47%, $P < 0.0001$); in patients with adequate surgical margins than in those with inadequate surgical margins (58% *vs* 46%, $P < 0.03$); in patients with good histologic response than in patients with a poor one (67% *vs* 48%, $P < 0.0001$); and in patients treated with neoadjuvant chemotherapy than in patients treated with adjuvant chemotherapy (61% *vs* 43%, $P < 0.0001$). According to single protocols, the 5-year EFS ranged between 42% for the first adjuvant protocol (IOS/OS-A1) and 67% for second (IOR/OS-N2) and fifth (IOR/OS-N5) neoadjuvant protocol. There were no significant differences in 5-year EFS between patients treated with different adjuvant protocols, however among patients treated with neoadjuvant chemotherapy, those treated with the first protocol (IOR/OS-N1) had a 5-year EFS rate significantly lower than those patients treated with the remaining 6 protocols. In the multivariate analysis (Table 5), of all prognostic factors for survival considered above, only serum values for alkaline phosphatase; type of chemotherapy; and histologic response to pre-operative treatment maintained their independent statistical significance.

3.5. Local recurrence

Although 106 (9%) patients had inadequate surgical margins, local relapse occurred in only 61 (5%) cases from 0.2 to 10 years (median 2 years) from the beginning of treatment. In all but 2 cases, local recurrence was combined with systemic relapse. In 32 patients, local recurrence occurred 3 to 28 months (median 8 months) before metastasis. In 19 cases metastases were diagnosed 4 to 32 months (median 11 months) before local recurrences and in 8 cases local and systemic relapses were contemporaneous.

The rate of local recurrence was 2.8% for patients treated with amputation; 6.2% for patients treated with limb salvage; and 5.3% for patients treated with rotationplasty. These differences were not however statistically significant. According to the surgical margins, the rate of local recurrence was significantly higher for patients with inadequate margins than in patients with adequate surgical margins (24.0% *vs* 3.6%, $P < 0.0001$). In patients treated with neoadjuvant chemotherapy, the rate of local recurrence was significantly higher in poor responders than in good responders (8.4% *vs* 3.9%, $P < 0.007$). Among patients with inadequate surgical margins and poor histological response, the rate of local recurrence was 31%.

3.6. Pattern of relapse

In patients who relapsed, 2 (0.4%) had local recurrence; 59 (12%) had local recurrence plus metastases; and 427 (88%) had metastases only. The first site of metastases was the lung in 436 patients (89%); other bones in 40 (8%); bone and lung in 2 patients; and other sites in 10 (2%). The average time to relapse was 21.3 months (range 2–204) and was significantly longer for patients with normal serum alkaline phosphatase values (18 *vs* 25 months, $P < 0.0001$); in patients treated with neoadjuvant chemotherapy than in patients treated with adjuvant chemotherapy (24 *vs* 16 months, $P < 0.0001$); and in good responders in comparison with poor responders (22 *vs* 17 months, $P < 0.03$). Around 15 (4%) patients relapsed 5 or more years after the beginning of chemotherapy and 6 after 10 or more years. Patients who relapsed between the fifth and tenth year

of treatment were diagnosed at the annual check-up with radiographs of the bone involved (which revealed local recurrence) and chest for lung metastases. Those who relapsed after 10 years presented with overt clinical manifestations leading to further radiological investigations.

3.7. Post-relapse treatment and outcome

The type of treatment performed to treat metastases in relapsed patients was not standardised but performed on an individual basis, that considered the site and the number of metastases; the length of the free interval; and the type of chemotherapy previously received by patients. The key point of treatment for patients followed by our institute was the surgical removal of metastases whenever possible. Second line chemotherapy with drugs not used in the adjuvant and neoadjuvant treatment; or with greater concentrations of previously used drugs was generally given in addition to patients in whom it was not possible to achieve complete surgical removal of metastases. The disease-free interval in these cases between the first treatment and relapse was shorter than 2 years and there were more than 2 metastatic lesions. After the first relapse, if further relapses occurred, patients were generally treated in other institutions.

At first relapse, 25 patients preferred to move to other centres for treatment and 7 others were lost to follow-up. From 456 patients treated at our institution: 365 had lung metastases; 30 relapsed with bone metastases; and 61 with local recurrence. Overall, the first treatment choice for relapse for patients treated at the institution was: surgery (43%), surgery combined with chemotherapy (42%), only chemotherapy (14%), and 10 patients (0.2%) had no specific treatment at all. Their 5-year EFS according to type of treatment was: 22.4% for patients treated by surgery and 17.8% for those treated with surgery and chemotherapy. Patients treated only by chemotherapy survived for 5 years. However, it must be taken into account that the patients treated only by chemotherapy were those with bigger, inoperable disease.

In detail, out of the 32 patients whose local relapse was the first relapsing event, the treatment was amputation or disarticulation in 26 cases; followed by second line chemotherapy in 16 patients; and a new limb salvage combined with chemotherapy in 6 patients. In two patients in whom local recurrences were not combined with systemic relapse, the treatment was an amputation followed by a second line chemotherapy. In the 19 cases where metastases were diagnosed before local relapse, the patients were locally treated by amputation in 6 cases and palliative radiotherapy in 9. In four patients, no local treatment was performed. In the 8 patients in whom local recurrence and metastases were contemporaneous, the treatment was amputation with simultaneous thoracotomy in 4 cases, and with no local treatment in the remaining 4. In the 59 patients in whom local relapse was combined with systemic relapse, the first site of metastasis was bone in 30 patients; lung in 25; and other sites in 4. The rate of bone metastases in the 59 patients who had local and systemic recurrences was significantly higher than in the 427 patients who had only systemic relapse (19% *vs* 7%, $P < 0.0001$).

The postrelapse outcomes of patients who had local and systemic relapse were: 55 died from 6 months to 10 years from local recurrence (median 17 months); and 4 survived with uncontrolled disease. In summary, 79 out of the 456 patients treated after their first relapse at our institute are currently still alive and free of disease (17%). More specifically, these patients consists of 71 (19%) who relapsed with lung metastases; 6 (15%) patients who relapsed with skeletal metastases; and 2 (3%) patients who relapsed with local recurrence.

3.8. Chemotherapy toxicity

Eighteen patients died from chemotherapy related toxicity. Of these deaths, 10 were due to doxorubicin-induced cardiotoxicity (cardiomyopathy and heart failure); 6 from sepsis during persistent leukopenia after cycles of cisplatin/doxorubicin; one to renal failure due to delayed methotrexate excretion; and one patient died of hepatic veno-occlusive disease after a cycle of methotrexate. All these patients, at the time of the death, were free of recurrence. Six of these patients received adjuvant and 12 were treated with neoadjuvant chemotherapy. In addition to the 10 patients who died for doxorubicin cardiotoxicity, 15 others experienced severe clinical cardiomyopathy cardiotoxicity. Of these 15 patients, 5 died from metastases, while 6 are alive and free of disease. The remaining 4 patients are alive and have been free of disease for 6 to 15 years after having a heart transplant. Doxorubicin cardiotoxicity was diagnosed from 1 week to12 years from the last cycle of chemotherapy. In the case with the 12-year latency period, the cardiomyopathy manifested clinically during the last month of the patient's first pregnancy. The cumulative dose in these 25 patients who had clinical doxorubicin cardiotoxicity was 480 mg/m^2 in 15 cases, 380 mg/m^2 in 7, and 320 mg/m^2 in 3 patients. In all cycles of chemotherapy performed, the incidence of WHO grade 4 neutropenia was 16%. The median duration of neutropenia was 8 days (range 2–20). Grade 4 thrombocytopenia, without associated episodes of bleeding, was reported in 2.4% of cycles. Admissions to hospital for treatment of febrile neutropenia or platelet transfusions were recorded after performing 0.9% cycles. However, as most of the patients lived far from the study centre, neutropenia in many cases were followed in other hospitals and occurrence rate may be underestimated.

Neurologic disturbance after ifosfamide was reported in 12 patients, all treated with high doses of these drugs.

Cisplatin related neuropathy or ototoxicity was reported only in 24 cases, probably due to continuous Cisplatin infusion over 72 h.

Episodes of WHO grade 1 to 2 renal toxicity was recorded in 0.6% after chemotherapy cycles. Lung tuberculosis controlled by medical treatment occurred in two patients, and one episode of transient ascites after the administration of the last cycle of methotrexate was observed.

Fertility was evaluated in a small subset of patients treated with neoadjuvant protocols and the results of which are published elsewhere [9,10].

3.9. Second tumour

Twenty patients had a second neoplasm which was diagnosed 1 to 14 years (median 6.1 years) from the beginning of treatment. These tumours were acute lymphoblastic leukemia (4); chronic myeloid leukemia (2); lung cancer (3); breast cancer (5); CNS tumours (2); soft tissue sarcomas (2); or renal cell carcinoma (1). The last patient had breast cancer 5 years after the end of chemotherapy. This patient was treated with mastectomy and further chemotherapy, and went on to reach complete remission. However, two years later she developed ovarian cancer and died from it after a year. Of the 24 cases who developed second tumours, 9 died of the second tumour and 11 are alive and free of disease from 2 to 17 years after diagnosis of the second neoplasm. It is important to underline that none of the 11 patients reported a familial cancer predisposition. More specifically, no patient family member had retinoblastoma, osteosarcoma or Li-Fraumeni syndrome. The patients with a second neoplasm received high-dose methotrexate, cisplatin, doxorubicin and ifosfamide in 3 cases; high-dose methotrexate; cisplatin, and doxorubicin in 16; and only methotrexate and cisplatin in one case.

3.10. Surgical complications

Around 410 surgical complications were observed in 378 patients, resulting in 33% of the patients having at least one complication while 32 patients had more than one complication. The rate of complications was 42% for the 817 patients treated with limb salvage; 31% for the 378 patients treated with rotationplasty; and 8% for the 289 patients treated with amputation. In 11 patients, it was necessary to perform amputation to treat deep infection resulting from surgical complications. The other cases were successfully managed without loss of the limb involved. However in 13 cases of prosthetic reconstruction, it was necessary to remove and substitute the implant. It must also be emphasised that complications also included 82 cases of polyethylene bush substitution in KMFTR prosthesis, which involved minor surgical procedures.

4. Discussion

The updated results from adjuvant and neoadjuvant studies reported here indicate the achievement of long-term EFS in approximately 60% of the 1148 study participants with osteosarcoma of the extremity. The patients were treated between March 1972 and June 1999 at Rizzoli Institute, Italy and followed for at least 5 years. Our results also indicate that late relapses and complications of treatment are not uncommon and we have detected some significant prognostic factors.

The main strength of our study is that all patients had been treated at the same institution by the same team of doctors and they had been followed for a minimum of 5 years unless they relapsed or died. Many papers about adjuvant and neoadjuvant protocols for osteosarcoma refer to multicentric studies, with all their inherent limitations, and the results are often reported in terms of probability of 5-year EFS, calculated on study population whose minimum follow-up was less than 3 years. The weak point is the elaboration of results achieved in patients treated over a 28-year period, and not in randomised series. During the span of the study, new drugs (ifosfamide); new radiological techniques (CT scan and REM); and new surgical reconstruction procedures (e.g., modular prosthesis) were introduced. In addition, it is possible that prognostic factors significant with one type of treatment may no longer be predictive with improved treatment.

Several and some times contradictory data have been reported in the literature regarding prognostic factors in non-metastatic osteosarcoma of the extremities treated with adjuvant or neoadjuvant chemotherapy [11,12]. Our present study concerning 1148 patients with non-metastatic disease, allowed the identification of 3 independent prognostic factors: serum values of alkaline phosphatase; type of chemotherapy performed; and in patients who received neoadjuvant treatment: histologic response to chemotherapy. It is interesting to note that if we considered only relapsing patients, there will be a correlation between the above mentioned prognostic factors and time of relapse. The prognostic significance of alkaline phosphatase in osteosarcoma is well known even before the chemotherapy era and has also been previously reported by our group [2], and this study has confirmed this in a large number of patients. It is also interesting to note that in our series, not only did the enzyme have a significant prognostic factor but, in patients with elevated values, there was also a correlation between serum alkaline phosphatase increment and prognosis. The correlation between histologic response to chemotherapy and outcome [7,8] has been confirmed in this study. This is in spite of the fact that in 3 of 6 of the neoadjuvant studies, poor responder patients received salvage chemotherapy with drugs not used pre-operatively. It therefore seems to be confirmed

that in poor responders, post-operative replacement salvage chemotherapy failed to improve the outcome of these patients.

Neoadjuvant chemotherapy is universally used in treatment of non-metastatic osteosarcoma. However, the question of whether neoadjuvant chemotherapy allows a higher rate of limb salvage and conveys survival benefit relative to adjuvant chemotherapy is controversial. In fact, rationales prefer neoadjuvant to adjuvant treatment as stated by Rosen et al. [8] in 1982 as it offered the surgeon the necessary time to have custom-made prosthesis; immediate treatment of microscopic disease; (adjuvant chemotherapy was usually started 4–5 weeks after conservative surgery); the opportunity to choose the most appropriate post-operative treatment according to the grade of necrosis observed in the resected specimen; and reduction of tumour mass making limb salvage easier, seem not to be valid anymore. In fact today, (a) new prostesis are immediately available and often other biological techniques of reconstruction instead of prosthesis, are often used; (b) chemotherapy, at our institution, is usually restarted 3–5 days after surgery; (c) post-operative salvage chemotherapy with different drugs before surgery was shown not to improve the prognosis of poor responder patients, such that all four drugs active in osteosarcoma (i.e., doxorubcicn, high-dose methotrexate, cisplatin, ifosfamide) are generally used regardless of the histological response; and (d) the higher number of limb salvage performed in patients who received neoadjuvant treatment seem to be due more to the possibility of better detection of tumour with CT scan and REM as well as the higher number of reconstructive solutions than to the reduction of the tumour mass than by pre-operative treatment. Moreover, the use of pre-operative chemotherapy could actually represent a risk of metastatic dissemination, during the 2–3 months of pre-operative treatment, for those patients (about 30%) who poorly respond to pre-operative chemotherapy. In this context, the use of adjuvant and neoadjuvant chemotherapy seems again to emerge as an open question. A small randomised recent study by the Pediatric Oncology Group [13] found no advantage of one over the other approach in localised extremity disease. However, we have some concerns about Goorin's paper [13] for the high number (50%) of amputations performed in both the adjuvant and neoadjuvant arms. The results of our series seem instead to indicate that a significantly high rate of local recurrence and 5-year EFS for patients treated with neoadjuvant chemotherapy in comparison with patients treated with adjuvant chemotherapy. Our results also indicate that neoadjuvant chemotherapy gave better local control. In fact, while there was a significantly higher percentage of local recurrence for those who had conservative surgery and treated with adjuvant protocols (12.2% *vs* 2.%, $P < 0.01$); in patients treated with neoadjuvant chemotherapy, there were no differences in local recurrence between limb-salvage and amputation (5.8% *vs* 3.3%, $P = 0.32$). However, it must be stressed that our revision is based on an unrandomised study. In our series, the rate of limb salvage was 71% and increased from 20% for patients treated with adjuvant chemotherapy between 1972 and 1982 to 90% for patients treated with neoadjuvant chemotherapy between 1983 and 1999. This rate of limb salvage is essentially the same as found for other mono-institutional studies concerning neoadjuvant treatment of osteosarcoma of the extremity (90% for Debré hospital [14], 80% for Gustave Roussy hospital [15] and Sloan Kettering [16], but is significantly higher in comparison with all the major multi-institutional trials (36% in the first 3 COSS studies [17–19]; 50% in Goorin's report [20]; and 43% in the Children's Cancer Group [21]). These differences are not surprising because in mono-institutional trials, patients are treated by a team of surgeons that take care of at least 30–50 new cases of osteosarcoma every year; while in multicentric trials, many patients are treated in institutions with very little experience in the treatment of musculoskeletal tumours. In our studies, in spite of the high numbers of limb salvages performed, the rate of local recurrence was relatively low (5%), with no significant differences between patients treated with amputation or rotationplasties; and patients treated with limb salvages. However, for patients with inadequate surgical margins, rate of local recurrence was 24% which increased to 31% for patients with inadequate surgical margins and poor histological response. These data are important, as already reported by us [22] and by other authors [23], that has been confirmed in this present study, the prognosis for patients with local recurrence is very poor, and significantly poorer than the outcome of patients who relapse with only metastases. In our series, the 5-year post-relapse EFS survival was 17% for patients who had only systemic relapse and 3% for patients who relapsed with local recurrence ($P < 0.004$). For this reason we believe that in osteosarcoma of the extremity, limb salvage procedures should be planned only when the pre-operative staging indicates that it is possible to achieve adequate surgical margins. If in spite of this, if pathological examination of the surgical specimen shows inadequate surgical margins, an immediate amputation should be considered especially if the histologic response to pre-operative chemotherapy is poor.

Treatment related-toxicity was high as approximately 1.5% of all deceased patients died from it. Approximately 40% of these deaths were caused by anthracycline cardiomyopathy. Since the frequency of clinical heart damage was observed to increase with time until the end of the anthracycline therapy, it is possible that incidence of doxorubicin cardiotoxicity could increase with longer follow-up. In this respect, it is important

to underline that one of the myocardiopathies observed in a female patient suddenly manifested during pregnancy 12 years after the end of treatment. In addition, the occurrence of a second malignant neoplasm in successfully treated osteosarcoma patients has become an area of increasing concern. In the present study, 20 of the 646 long-term survivor patients (3%) developed a second neoplasm. Since second malignancies are usually late events (8 of 20 second neoplasm in this study were observed more than 10 years after the beginning of treatment), it is possible that the incidence of a second neoplasm increases with longer follow-up.

The increment of limb salvage procedures and the better long-term survival of patients with non-metastatic osteosarcoma of the extremity treated with combined therapy, results in a higher rate of immediate and delayed surgical complications. In our series, 42% of patients treated with limb salvage had some major surgical complications and had to be reoperated once or more times. We believe that in planning limb salvage procedures for osteosarcoma of the extremity, besides the concerns for local recurrence, the concerns for complications and functional results should be considered also, and that they have to balance the surgical challenge of saving a limb. In other words, for each patient a rational solution must be found, in order to obtain optimal functions with minimal risk of local recurrence and surgical complications.

In conclusion, in association of chemotherapy with surgery at our institution, it was possible to increase the long-term survival of osteosarcoma of the extremity from 20% during the pre-chemotherapeutic era to more than 60%. In addition, while in the past almost all patients were amputated, today it is possible to spare the limb in more than 90% of patients. Unfortunately, over the past 15 years, the rate of disease-free survival and overall survival seems to be have been stable (62% between 1986 and 1989 and 66% for patients treated between 1997 and 1999 in our studies). New drugs and/therapies are therefore necessary for the greater improvement of these results, because it is difficult to accept that simple modification of drug regimens used in present chemotherapy protocols will be able to improve these survival rates more.

Conflict of interest statement

None declared.

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