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Pattern of relapse in patients with osteosarcoma of the extremities treated with neoadjuvant chemotherapy

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Abstract

570 patients with osteosarcoma of the extremities were treated with five different protocols of neoadjuvant chemotherapy at Rizzoli Institute between 1983 and 1995. Surgery consisted of limb salvage in 83% rotation plasty in 5% and amputation in 12%. The 5-year event-free survival (EFS) was 60% which varied according to the protocol followed, ranging from 47.6% to 66.4%. 234 patients relapsed. The pattern of relapse was analysed. The mean relapse time was 23.8 months (range: 2–96). The first site of systemic relapse was the lung in 88% (32% of these had less than three pulmonary metastases and 68% three or more), bone in 9%, lung and bone in 2% and other sites in 3%. The relapse time and the number of pulmonary metastases were strictly correlated with the efficacy of the protocol of chemotherapy used. Patients treated with the three protocols that gave a 5-year EFS of more than 60% relapsed later and had fewer pulmonary lesions than patients treated with the two protocols that gave a 5-year EFS of 47.6% and 52.5%. The rate of local recurrence was relatively low (6%). This was not correlated with the protocol or the type of surgery used: limb salvage (6.4%), rotation plasty or amputation (4.1%). However, the rate of local recurrence was very high (21.9%) in the few patients (7%) that had less than wide surgical margins. We conclude that for patients with osteosarcoma of the extremities treated with neoadjuvant chemotherapy: (a) the pattern of systemic relapse changes according to the efficacy of the protocol of chemotherapy used. This should be always considered when evaluating the preliminary results of new studies as well as in defining the time of follow-up; (b) limb salvage procedures are safe and do not jeopardise the outcome of the patient, provided that wide surgical margins are achieved.

Keywords: Systemic relapse; Osteosarcoma; Chemotherapy

1. Introduction

Following the introduction of adjuvant chemotherapy, in the early 1970s, the long-term outcome for patients with high-grade osteosarcoma of the extremities has dramatically improved with survival rates rising from 10–15% to 50–60% [1–5]. However, in most of these patients, the surgical treatment was still amputation. In the early 1980s, adjuvant chemotherapy was substituted by neoadjuvant chemotherapy that enabled limb-sparing segmental resections instead of cross bone amputations in most patients [6–11]. In addition, at the same time, the regimens of chemotherapy improved, and new drugs, such as cisplatin and ifosfamide, were added to high-dose methotrexate, doxorubicin and bleomycin–cyclophosphamide–dactinomycin (BCD).

Comparing the results of adjuvant treatments with the results of historical controls, some authors have reported that the combination of chemotherapy and surgery not only improved the cure rate, but also modified the pattern of metastases.

In comparison with patients treated with surgery alone, patients treated with adjuvant chemotherapy relapsed later and with fewer pulmonary metastatic nodules [12,13]. These findings were confirmed in a randomised study [14]. Moreover, in some series of

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patients treated with adjuvant chemotherapy, there were also differences in the site of the first metastases, with an increment of metastases located in the bone [15,16].

For patients treated with neoadjuvant chemotherapy, there are no data in the literature specifically regarding the pattern of relapse. The purpose of this paper was to evaluate this pattern in 234 patients with osteosarcoma of the extremities who relapsed after a neoadjuvant treatment. This treatment was administered at our institute between 1983 and 1995, using five different protocols of chemotherapy activated at different times.

2. Patients and methods

570 patients, under 40 years old, with primary high-grade osteosarcoma located in the extremities, without detectable metastases at presentation, were treated with neoadjuvant chemotherapy at our institute between March 1983 and June 1995.

The diagnosis of osteosarcoma, established by clinical and radiological findings, was always confirmed by histological slides of tumour tissue from biopsies and resected specimens.

A complete history was made of all the patients. They also underwent a thorough physical examination and several chemical laboratory tests. The primary tumour was evaluated on plain radiographs, Technetium 99 methylene diphosphonate (MDP) bone scan, angiogram, computer tomography (CT) scan and, in the more recent cases, with magnetic resonance imaging (MRI). Bone metastases were searched for with total body scan, whereas chest radiograms and CT scan were used to investigate the lungs. The CT equipment used to detect lung metastases in the preoperative staging and during the follow-up was the 'CT Sytec 300' (GE, Milwaukee, USA) from 1983 to 1994, and afterwards the 'GE High Speed' (GE, Milwaukee, WN, USA). Tumour size was estimated using CT scan measurements of the three diameters of the lesion, according to the method reported by Gobel and colleagues [17]. The volume of the tumours with extraosseous extension was calculated assuming an ellipsoidal configuration, while for diaphyseal tumours without extraosseous extension, the volume was calculated assuming the configuration of a cylinder. The formulae used to obtain the value of the volume, expressed in ml, were respectively $a \times b \times c \times 0.52$ and $a \times b \times c \times 0.785$.

Neoadjuvant chemotherapy was performed according to five different protocols successively activated. These protocols of chemotherapy, reported in detail in previous papers [9,18–20], are shown in Table 1.

During chemotherapy, besides the clinical evaluation, patients were checked every two months with radiographs of the chest and the treated limb. Additional investigations, such as CT scans of the chest, were performed only if there was a clinical and/or radiographical suspicion of relapse. After completion of chemotherapy, patients were followed up in the outpatient clinic with the above mentioned radiograms every two months for two years, every three months in the third year, and subsequently every six months.

3. Results

3 patients died during the preoperative treatment, 2 of chemotherapy related toxicity and 1 committed suicide. In the remaining 567 patients, surgery consisted of limb salvage in 470 (83%), amputation in 67 (12%) and rotation plasty in 30 (5%). The surgical margins, classified according to Enneking's criteria [21] were adequate (radical or wide) in 526 patients (93%) and inadequate (marginal, intralesional or contaminated) in 41 (7%).

Table 1
Summary of protocols of chemotherapy

Protocol 1	Preoperative	MTX–CDP(i.a.)	
(3/83–8/86)	Postoperative	Good responders	ADM–MTX–CDP MTX–CDP
		Poor responders	ADM–BCD
Protocol 2	Preoperative	MTX–CDP(i.a.)/ADM	
(9/86–12/89)	Postoperative	Good responders	ADM–MTX–CDP
		Poor responders	ADM–IFO–MTX–CDP/ET
Protocol 3	Preoperative	MTX–CDP (i.a.)/ or ev ADM	
((1/90–8/91)	Postoperative	Good responders	MTX–CDP/ADM
		Poor responders	MTX–IFO–CDP/ADM
Protocol 4	Preoperative	MTX–CDP(i.a.)/ADM	
(9/91–12/92)	Postoperative	Good and poor responders	MTX–IFO–CDP/ADM
Protocol 5	Preoperative	MTX–CDP (i.a. or i.v.)/ADM–IFO/ADM-CDP(i.a. or i.v.)/IFO	
(1/93–6/95)	Postoperative	Good and poor responders	ADM–MTX–CDP–IFO

MTX, methotrexate; ADM, doxorubicin; CDP, cisplatin; IFO, ifosfamide; ET, etoposide; CDP/ADM in association; CDP/ET, in association; IFO/CDP in association; IFO/ADM in association CDP was preoperatively delivered or intra-arterially (i.a.) or intravenously (i.v.).

Tumour response to chemotherapy, histologically evaluated following the criteria previously reported [22], was good (90% or more tumour necrosis) in 370 patients (65%) and poor in 197 (35%).

At a median follow-up of 10 years (range: 4.5–16.5), 327 patients remained continuously free of disease (58%), 234 relapsed (41%) and 6 died of chemotherapy-related toxicity (1%). The 5-year event-free survival (EFS) and overall survival (OS) were, respectively, 59.0% and 65.7%.

As reported in Table 2, the rate of 5-year EFS was quite different in the five protocols, ranging between 47.6% and 66.4% ($P < 0.03$). Patients treated according to protocols 2, 4 and 5 had a significantly better prognosis than patients treated according to protocol 1 and 3 (5-year EFS of 66.4%, 61.6%, 65.0% versus 47.6% and 52.5%). According to the type of surgery, the 5-year disease-free survival rate was significantly higher in patients treated with limb salvage than in patients treated with amputation or rotation plasty (62.5% versus 48.4%; $P < 0.03$).

For the purpose of this paper, we considered only the 234 patients who had relapsed, and we evaluated: (a) the site (or sites) of first relapse and, in case of lung metastases, the number of pulmonary nodules on CT scan; (b) the interval between the beginning of chemotherapy and the time of first relapse.

The 234 patients who relapsed did so with metastases in 200 (85%) cases, with local recurrence combined with metastases in 32 (14%) cases, and with local recurrence only in 2 (1%) cases.

3.1. Time to relapse

The mean time to relapse was 23.8 months (range 2–96), and 141 patients (60%) relapsed within 2 years from the beginning of treatment. As shown in Table 3, the time to relapse was not related to sex/age of patients, histology, volume/site of the tumour or the presence of pathological fracture at presentation. The time to relapse was not related to type of surgery or to the histological response to preoperative chemotherapy. The time to relapse was instead significantly related to the serum levels of alkaline phosphatase at presentation (26.3 months for patients with normal values versus 22.2 months for patients with high values; $P < 0.005$) and, as reported in detail below, to the protocols of chemotherapy.

3.2. Local recurrence

The rate of local recurrence was 6% (34/370), and was unrelated to the gender/age of the patients, histology, site/volume of the tumour, presence or not of pathological fractures, or the serum level of alkaline phosphatase. According to the type of surgery, the local recurrences were 4.1% (1/30) for patients treated with amputation or rotation plasties and 6.4% (30/470) for patients treated with limb salvage. This difference was not statistically significant. As regards chemotherapy, the 5-year local recurrence rate was 5.5%, 3.0%, 8.2%, 6.6% and 8.4% in the five protocols, respectively. These differences were also not statistically significant. Local recurrences did correlate, however, with the quality of the surgical margins and with the histological response to chemotherapy.

With regard to the surgical margins, the 5-year local recurrence rate was 4.7% for patients with adequate surgical margins and 21.9% (3/41) for patients with inadequate surgical margins ($P < 0.0001$). According to the histological response to chemotherapy, the rate of local recurrence at 5 years was 4.2% for the 354 good responder patients and 9.6% for the 196 poor responder patients ($P < 0.01$). In multivariate analyses, surgical margins (relative risk 3.2; $P < 0.0001$) and response to chemotherapy (relative risk 1.6; $P < 0.05$) were independent prognostic factors of local recurrence.

Table 2
5-year event-free survival (EFS), time and site of first relapse and number of pulmonary metastases according to the protocols of chemotherapy

Protocol *n* (%)	5-year EFS	No. of patients who relapsed *n* (%)	Mean time to relapse	Patients who relapsed within 2 years *n* (%)	Patients who had the first relapse in the lungs *n* (%)	Patients who relapsed in the lung with less than three metastases *n* (%)
Protocol 1 127 (22)	47.6%	66 (52)	15.6 months	55 (83)	61 (92)	9 (15)
Protocol 2 164 (29)	66.4%	59 (36)	26.6 months	31 (53)	53 (90)	21 (40)
Protocol 3 98 (17)	52.5%	45 (46)	22.9 months	28 (62)	40 (89)	12 (30)
Protocol 4 60 (11)	61.6%	24 (40)	29.0 months	8 (33)	19 (79)	10 (53)
Protocol 5 121 (21)	65.0%	40 (33)	26.8 months	19 (48)	33 (83)	14 (42)
	$P < 0.03$			$P < 0.0001$	*P* NS	$P < 0.004$

NS, non-significant.

3.3. Site and number of first metastases

The first sites of metastases were the lung in 202 patients (86%), bones in 21 (9%), simultaneous lung and bone in 5 (2%), lymph nodes in 3 (1%), heart in 2 (1%) and epidural in 1 (0.4%). The site of first systemic relapse (Table 3) was not related to a gender/age of patients, histology, volume/site of primary tumour, serum values of alkaline phosphatase, the presence of pathological fracture, type of surgery or histological response to preoperative treatment.

The interval between start of treatment and relapse was essentially the same for patients with first metastases located in the lung, (23.6 months), in bone (22.2 months), or in other sites (27.0 months).

In patients who relapsed with metastases located outside the lung there was only one metastatic lesion at the time of the first relapse. In patients who relapsed with lung metastases the mean number of nodules found at the time of first relapse was 3.24 (range: 1–8). In 66 (32%) patients, the number of lung nodules were one or two and in 141 (68%) the number was three or more. As shown in Table 3, there were no differences in the rate of patients who had less than three pulmonary nodules according to the gender/age of patients, histology, site/size of the primary tumour, type of surgery presence of pathological fracture and histological response to chemotherapy. Concerning alkaline phosphatase, the rate of patients who had less than three pulmonary nodules at the time of the first relapse was significantly higher in those with normal serum values of this enzyme than in those with high values (41 versus 24%; $P < 0.008$).

3.4. Time and site of metastatic relapse according to the protocols of chemotherapy

As indicated in Table 2, there seems to be a correlation between the time to relapse and the rate of EFS achieved by the protocol of treatment. The mean time to relapse was, in fact, significantly shorter in patients treated according to protocols 1 and 3, that gave a 5-year EFS of only 47.6% and 52.5% respectively, than in patients treated according to protocols 2, 4 and 5, in which the 5-year EFS rates were 66.4%, 61.6% and 65.0%, respectively. This correlation between the time

Table 3
5-years EFS, time to relapse, site of first relapse and number of pulmonary metastases according to several variables

Variables	5-year EFS	No. of patients who relapsed $n = 234$ n (%)	Mean time to relapse (months)		Patients who had the first metastases in lung n (%)		Patients who relapsed in the lung with less than three metastases n (%)	
Gender								
Male	59.2%	137 (59)	23.1	P = NS	118 (86)	P = NS	41 (35)	P = NS
Female	61.0%	97 (41)	25.3		89 (92)		25 (28)	
Age (years)								
< 15	55.6%	135 (58)	24.3	P = NS	122 (90)	P = NS	38 (31)	P = NS
> 15	64.8%	99 (42)	23.6		85 (86)		28 (33)	
Histotype								
Osteoblastic	50.3%	172 (74)	22.3	P = NS	155 (90)	P = NS	47 (30)	P = NS
Others	70.8%	62 (26)	28.5		52 (84)		19 (37)	
SAPH[a]								
Normal	66.1%	108 (46)	26.3	$P < 0.005$	97 (89)	P = NS	40 (41)	$P < 0.008$
Elevated	52.9%	126 (54)	22.2		110 (87)		26 (24)	
Tumour volume[d]								
< 150 ml	66.9%	82 (35)	25.7	P = NS	68 (83)	P = NS	21 (31)	P = NS
> 150 ml	54.1%	152 (65)	23.2		135 (89)			
Site[b]								
Proximal	58.1%	160 (68)	23.6	P = NS	137 (86)	P = NS	40 (29)	P = NS
Distal	65.5%	74 (32)	24.5		70 (95)		26 (37)	
Pathological fracture								
Yes	53.7%	39 (17)	21.3	P = NS	36 (92)	P = NS	10 (28)	P = NS
No	61.0%	195 (83)	24.5		171 (88)		56 (33)	
Surgery								
Amputation[c]	48.4%	51 (22)	21.6	P = NS	46 (90)	P = NS	14 (30)	P = NS
Limb salvage	62.5%	183 (78)	24.7		161 (88)		52 (32)	
Histological response								
Poor	47.1%	109 (47)	22.3	P = NS	98 (89)	P = NS	27 (28)	P = NS
Good	67.0%	125 (53)	25.6		109 (87)		39 (36)	

[a] SAPH, serum alkaline phosphatase.
[b] Proximal: femur and humerus; Distal, tibia, fibula, ulna, radius.
[c] Including 30 rotation plasties.
[d] Data available for only 553 patients.

to relapse and the efficacy of the protocol of chemotherapy is also indicated by the rate of patients who relapsed within the first 2 years of the beginning of treatment. In fact, the percentage of relapses within the first 2 years was significantly higher ($P < 0.0001$) in patients treated according to protocols 1 and 3 (83% and 62%) than in patients treated according to protocols 2, 4 and 5 (53%, 33% and 48%).

Regarding the site of first relapse, in patients treated according to the more effective protocols, the percentage of extrapulmonary metastases was higher than in patients treated with the less effective protocols (14.6% versus 9.0%). This difference, however, was not statistically significant.

4. Discussion

In past studies, investigators comparing the outcome of patients with osteosarcoma of the extremities treated with adjuvant chemotherapy with historical controls, found out that adjuvant treatment improves not only the cure rate, but also delays the time of first recurrence in relapsing patients. Moreover, adjuvant chemotherapy also reduces the number of lung metastases at the time of pulmonary relapse, making these patients more suitable for salvage therapy by mastectomy [12,13]. These results were confirmed by the controlled multi-institutional study MIOS, in which patients were randomised to be treated by surgery alone or by surgery plus adjuvant chemotherapy. Evaluating the pattern of relapse of this study, Goorin and associates [14], reported that patients treated with surgery alone relapsed earlier and had more pulmonary nodules than those treated with post-surgical adjuvant chemotherapy. In osteosarcoma of the extremities, adjuvant chemotherapy was also reported to modify the pattern of relapse by increasing the rate of bone metastases [15,16]. This finding, however, was not confirmed by the previously mentioned retrospective [12,13] and prospective [14] studies.

The results of our study confirm that surgery combined with chemotherapy delays the time to relapse. For the 234 patients who relapsed (200 with metastases, 32 with metastases and local recurrence and 2 only with local recurrence) the mean interval from the beginning of treatment and the appearance of the first recurrence was 23.8 months (range: 2–96). This interval is significantly longer than the one observed in our 92 patients treated between 1959 and 1970 who relapsed after surgical treatment alone (mean time to relapse 7.7 months) [1], and 5.4 months for the 35 patients treated from 1980 to 1991 [13].

The interval between the start of treatment and relapse of the present study was also significantly longer than the interval (18.1 months) observed in the 76 patients treated with adjuvant chemotherapy between 1980 and 1990 [13]. It is important to stress that in this series of patients treated only with surgery or with surgery followed by adjuvant chemotherapy, the rate of 5-year EFS was significantly lower than the rate observed in the series of patients treated with neoadjuvant chemotherapy reported in this study (12.4% and 45.5% versus 59%).

In this report, the time to relapse was significantly correlated with the serum levels of alkaline phosphatase and to the protocol of chemotherapy. Patients with high serum levels of alkaline phosphatase at presentation relapsed earlier than patients with normal values of this enzyme. With regard to chemotherapy, the patients of the present study were treated with five different protocols successively activated over a 13-year period. The results obtained in these trials were quite different. In fact, in the different protocols, the 5-year EFS ranged from 47.6% to 66.4% ($P < 0.03$). The time taken to relapse in the 234 patients treated with neoadjuvant chemotherapy was longer in the more effective protocols (i.e. the protocols that gave the higher rate of 5-year EFS) than the less effective ones. The rate of patients who relapsed within the first 2 years from the start of treatment was, in fact, significantly higher in the group of patients treated with the less effective protocols of chemotherapy. On the basis of these data we believe that the difference in the time to relapse observed in patients of the present study treated with neoadjuvant chemotherapy and in patients of the previous adjuvant chemotherapy studies was probably due not to the difference in times when chemotherapy was applied (only after surgery in the adjuvant group, and before and after surgery in the neoadjuvant group), but to the higher efficacy of the more recent and more complex neoadjuvant protocols. In addition, we found that with the more effective protocols, besides delaying recurrence time, resulted in the number of patients with pulmonary metastases being generally lower. In fact, the number of patients that had only one or two metastatic nodules, at the time of the first pulmonary relapse, was significantly higher in the group of patients treated with the more effective protocols.

Regarding the site of first relapse, in the present neoadjuvant series the lung continued to be the site most commonly involved. It was involved in 86% (88% including bone + lung cases), which was not significantly different from the rate observed in our previous series of patients treated by surgery alone (94%) or by surgery plus adjuvant chemotherapy (95%). In this series, the number of patients whose first relapse was in the lung was similar in the five different protocols.

These results seem to indicate that there is a close correlation between the use of aggressive chemotherapy and the considerably longer time to relapse, and the significantly lower number of lung metastases. They also indicate that chemotherapy also has some effect in

patients who relapse and should always be considered in evaluating the preliminary results of new neoadjuvant protocols and in defining the time of follow-up of these patients, time that should be extended to 5 years at least.

In recent years, the number of patients with osteosarcoma of the extremities treated with limb salvage, instead of amputation, has been on the increase [13,20,23,24]. However, it is not yet clear whether the risk of local recurrence is greater or not in patients treated with less extensive surgery and neoadjuvant chemotherapy. In fact, while some multicentric and single centre studies showed a local recurrence rate after limb-sparing resections that was three to four times higher than after amputation [25–28], in two recent reports [23,24] no differences in terms of local recurrence were observed comparing-limb sparing surgery with amputation. In this study, there were no significant differences in the rate of local recurrences between patients treated with amputation or rotation plasties (4.1%) and patients treated with limb salvages (6.4%). The rate of local recurrence was not correlated with the protocol of chemotherapy either.

As previously reported by us [29] and by others [24,28], the rate of local recurrences was instead significantly correlated with surgical margins and with the histological response to chemotherapy. In particular, for those 41 patients (7%) with less than wide surgical margins, the rate of local recurrence was very high (21.9%). From these data, we could conclude that in osteosarcoma of the extremities limb salvage procedures combined with neoadjuvant chemotherapy are safe and do not jeopardise the outcome of patients, provided that wide surgical margins are achieved. However, due to the high rate of local recurrence observed in patients (in our study) with less than wide margins of resection, accurate pathological examination of surgical margins must be performed in every patient with osteosarcoma surgically treated with limb salvage, and in the rare cases when the surgical margins are inadequate, a secondary amputation should always be considered.

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