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Long-Term Evaluation of Surgery Followed by Adjuvant Adriamycin in Osteogenic Sarcoma

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Abstract—*From* 1974 *to* 1978 29 *consecutive patients with operable oesteogenic sarcoma entered* 2 *successive clinical trials of adjuvant chemotherapy with adriamycin (ADM) alone. Following radical surgery the first group of* 14 *patients received ADM* 75 mg/sqm q 4 *weeks for a total of* 8 *doses, the second group received ADM* 30 mg/sqm *daily for* 3 *days every* 4 *weeks for a total of* 6 *cycles. All patients belonging to the first group underwent amputation or exarticulation, while in* 4 *of* 15 *of the second group a limb-sparing surgery was performed. Lung tomograms as well as bone scans were not mandatory in the initial work-up. Follow-up ranged from* 7 *to more than* 11 *years. Thirteen patients* (45%) *remain continuously relapse-free survivors:* 4 *of* 14 (28.5%) *in the first group and* 9 *of* 15 (60%) *in the second group. This difference is not statistically significant. The longest free interval in the* 16 *patients relapsed was* 32 *months. Severe toxicity from ADM was observed in only* 1 *patient and consisted of reversible cardiomyopathy. ADM alone as postoperative adjuvant chemotherapy for osteogenic sarcoma achieved results comparable to those obtained by other contemporary more complex regimens of combination chemotherapy.*

INTRODUCTION

In the last 10 years the administration of adjuvant chemotherapy following radical surgery for osteogenic sarcoma (OS) has been a common therapeutic modality. Adriamycin (ADM), methotrexate given at high doses (HDMTX) and, more recently, cisplatin have been established to be the most effective drugs and were commonly used both as single agents and in combination as adjuvant chemotherapy [1–4] with the main aim of improving the 20% cure rate achievable with surgery alone [5]. Other drugs, such as cyclophosphamide, vincristine, dactinomycin, bleomycin, imidazol carboxamide and melphalan were also utilized in several adjuvant regimens, however despite the differences in the number of drugs utilized, in their combinations and in the schedules of administration, the 2–3 year continuous relapse-free survival (CRFS) levelled around 50% in all series with very few exceptions [6–10].

In 1978 we published the results of an ongoing study with postoperative ADM as single agent adjuvant chemotherapy in a small series of patients with OS, reporting a 53% 2-year CRFS rate [11].

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The aim of this study is now to update the results obtained in the whole series of patients treated at that time with ADM alone following radical surgery in OS, because the long period of follow-up, in excess of 7 years for each patient, allows one to draw conclusions in terms of disease-free survival.

PATIENTS AND METHODS

From April 1974 to December 1978, 29 consecutive patients with a histological diagnosis of classic osteogenic sarcoma of the extremities were treated with radical surgery of the primary tumor followed by adjuvant chemotherapy with ADM alone. ADM was administered in 2 different modalities. The first group (ADM 75) of 14 consecutive patients received the drug as a single intravenous dose of 75 mg/sqm every 4 weeks for a total of 8 cycles. Starting on April 1977, the second group (ADM 90) of 15 consecutive patients was given ADM at the dose of 30 mg/sqm intravenously daily for 3 consecutive days every 4 weeks for a total of 6 cycles.

Patients' clinical features are summarized in Table 1, as well as the type of surgical procedures adopted. All patients of the first group underwent amputation or exarticulation. Four patients of the second group underwent conservative surgery, with en-bloc resection and prosthetic replacement of

Table 1. *Clinical data*

	All patients	First group (ADM 75)	Second group (ADM 90)
Patients	29	14	15
Sex (M/F)	16/13	8/6	8/7
Median age (years months)	13	13.5	12.8
Age range	5–45	7.5–40	5–45
Location of the primary			
Distal femur	13	5	8
Proximal femur	1	0	1
Proximal tibia	8	6	2
Fibula	2	1	1
Proximal humerus	2	1	1
Radius	2	1	1
Metatarsus	1	0	1
Type of surgery			
Transmedullary amputation	11	4	7
Above prox. joint amputation	4	2	2
Exarticulation	10	8	2
Resection	4	0	4

proximal and distal femur respectively in 2 cases, resection of the third metatarsus in 1 case and resection of the upper part of the fibula followed by radiation therapy (68 Gy) in the last case.

In the period of this study full lung tomography and bone scan were not mandatory in the routine pre-surgical evaluation procedures, and were performed only in the presence of specific diagnostic doubts. Therefore lung tomograms were carried out only in 2 patients of the first group treated with ADM at 75 mg/sqm and in 5 patients of the second group treated with ADM at 30 mg/sqm daily for 3 days. Similarly, bone scans were utilized as part of the initial work-up in 1 and in 5 patients, respectively.

ADM was administered at the planned full dose in 9 of the 14 patients of the first group (ADM 75) and in 13 of the 15 patients of the second group (ADM 90). In the remaining patients 90% of the planned total dose has been given because of dose reduction related to myelosuppression.

Besides routine blood chemistry and EKG, follow-up procedures included radiograms of the chest, and of the stump in cases of transmedullary amputation or conservative surgery, every 4 weeks during the first year from surgery, every 8 weeks during the second and third year, and every 3–4 months afterwards. After the fifth year from surgery patients have been checked once yearly.

The relapse-free interval was calculated as the time elapsed from surgery to the first appearance of metastases or recurrence, or to the time of the last follow-up visit.

RESULTS

Thirteen of the 29 evaluable patients (45%) are alive and continuously relapse-free after a median follow up of 103 months (range 84–141). In the first group (ADM 75) 4 of the 14 patient (28.5%) are alive and relapse-free as compared to 9 of 15 (60%) in the second group (ADM 90). Results are summarized in Table 2.

Sixteen patients (55%) relapsed after a median interval of 9 months (range 1–32) from surgery (Fig. 1). First relapse was represented by the occurrence of lung metastases in 11 cases, of simultaneous lung and bone metastases in 2 cases and of skeletal metastases in 3 cases, one of which was at the level of the femoral stump. Four patients of the first group (ADM 75) and 1 of the second group (ADM 90) relapsed during the period of administration of the adjuvant chemotherapy. All the patients who relapsed died of their disease in a median time, after relapse, of 7 months (range 4–21 months).

Of the 14 patients with the primary tumor located in the femur, 1 of 5 (20%) of the first group (ADM 75) and 4 of 9 (44.5%) of the second group (ADM 90) were CRFS (Fig. 2). Of the 15 patients with primary tumor located in skeletal segments other than femur, 3 of 7 (43%) in the first group (ADM 75) and 5 of 6 (83%) of the second group (ADM 90) were CRFS.

Of the 11 patients subjected to transmedullary amputation, 1 had local recurrence at the level of the femoral stump. None of the 4 patients treated with conservative surgery relapsed, either locally or in distant sites.

Table 2. Clinical results

	No.	CRFS	Time to relapse (months) Median	Range
All patients	29	13 (45%)	9	1–32
First group (ADM 75)	14	4 (28.5%)	9	1–32
Second group (ADM 90)	15	9 (60%)	9.5	5–14
Patients with primary tumor of the femur	14	5 (37.5%)	8	1–24
First group (ADM 75)	5	1 (20%)	7	1–24
Second group (ADM 90)	9	4 (44.5%)	8	5–14

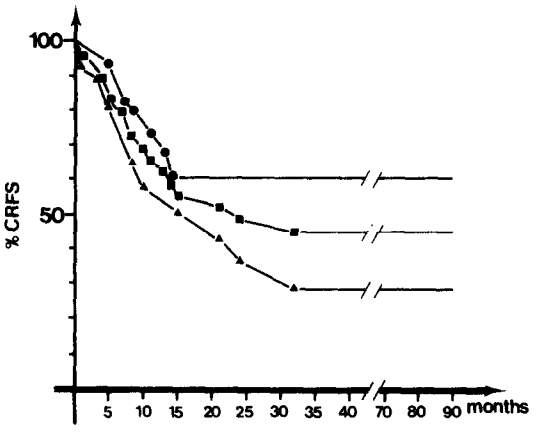

Fig. 1. Continuous relapse-free survival: ■ *all patients;* ▲ *first group treated with ADM* 75 mg/sqm; ● *second group treated with ADM* 90 mg/sqm.

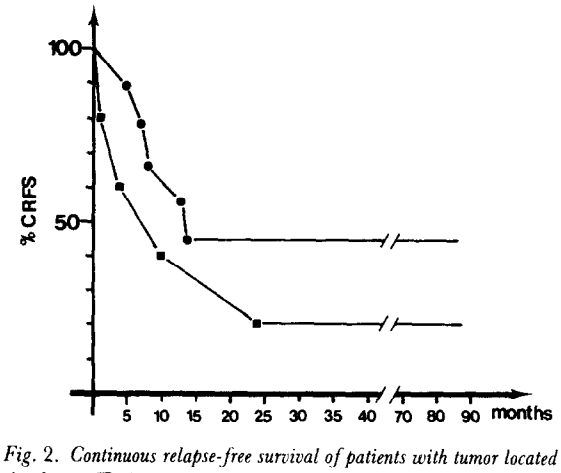

Fig. 2. Continuous relapse-free survival of patients with tumor located in the femur: ■ *first group treated with ADM* 75 mg/sqm; ● *second group treated with ADM* 90 mg/sqm.

Toxicity from this chemotherapeutic regimen was minimal and consisted mainly of nausea and vomiting, completely reversible hair loss, and mild transient episodes of myelosuppression. Only 1 patient, an 11-year-old girl, developed a congestive heart failure 1 month from the end of chemotherapy. After a 12 month therapy with cardiac glycosides and diuretics, complete clinical and functional recovery has been obtained and no further signs of cardiac abnormality have been observed so far.

DISCUSSION

The 45% CRFS rate obtained in our series treated with surgery and post-operative ADM alone is similar to that obtained with the majority of more complex regimens used in several clinical trials [6, 12, 13].

The survival rate of our series can be considered a true cure rate since the minimum follow-up is in excess of 7 years. This compares favorably with most reported series with shorter follow-up and is well-superimposable to that obtained by Cortes *et al.* with the same treatment modality [1].

One of the major criticisms to the interpretation of data from non-randomized trials of adjuvant chemotherapy for OS was based on the fact that the improved survival obtained, as compared with historical controls, might be dependent on a selection of favorable patients through the adoption of more accurate stageing procedures, consisting mainly of the routine use of pre-operative lung tomography, computerized tomography of the chest, and of bone scan [14]. These diagnostic procedures were not applied to the patients included in this study, and therefore some cases with minimal metastatic disease could have been included, as is suggested by the appearance of lung metastases in a patient of the first group (ADM 75) after 1 month from surgery.

The difference in CRFS rates between the 2 groups of patients (28.5% vs. 60%) suggests that a higher dose of ADM could achieve better results. However, this difference is not statistically significant. This study was not randomized and consisted of 2 successive consecutive series of patients treated with the same drug given at different dose levels. For this reason the 2 groups are not fully comparable. Prognostic parameters such as age, sex, location of the primary tumor and type of surgery are not in favor of the second group (ADM 90) who achieved better results in terms of CRFS. Considering only the patients with primary tumor located in the femur the CRFS rate is still in favor of the second group (ADM 90) (44.5% vs. 20%). This figure is even more evident when primary sites other than femur are considered (83% vs. 43%).

The aim of updating the results obtained with ADM alone as adjuvant chemotherapy for OS was not the comparison of the efficacy of the two different modalities of administration, but the evaluation of the 'cure rate' obtained with such an approach in a consecutive series of patients with osteogenic sarcoma of the extremities. ADM is a drug easy to administer in an out-patient setting and devoid of severe toxicity provided that well-established precautions are observed, especially a close monitoring of the cardiac functions when a total dose of 550 mg/sqm [15] is planned. ADM, when given at the maximally tolerated dose, could achieve results comparable, in terms of disease-free survival, to other contemporary more complex chemotherapeutic regimens that were used in the 1970s for the adjuvant therapy of osteogenic sarcoma.

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