Limb Salvage in Osteogenic Sarcoma of Extremities: A New Therapeutic Approach Associating Infusion and Hyperthermic Antiblastic Perfusion

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Keywords: chemotherapy; perfusion, extremity

Abstract

***(J. Extra-Corpor. Technol.* 19[3] p. 338-347 Fall 1987, 49 ref.) From August 1983 to September 1986, 17 patients affected by osteogenic sarcoma of extremities were admitted to our Division with only surgical alternatives of amputation or disarticulation due to the impressive local extension of disease.**

Trying to avoid this procedure we started a program of limb salvage as follows: two cycles of intra-arterial cis-platinum (CCDP) plus systemic high dose of methotrexate (HDMTX) followed by hyperthermic antiblastic perfusion (HAP) with high dose CDDP and for the majority of patients 2 more cycles of systemic HDMTX + CDDP with or without radiotherapy on the primary.

Immediate response, evaluated both in terms of necrosis and of clinical and radiologic reduction of the tumor mass, was so impressive that in 10 patients it was possible to perform a conservative surgery, en bloc resection of the primary tumor plus endoprosthesis, with a satisfactory functional and cosmetic result.

None of the patients relapsed locally; 8 developed lung metastases that, whenever possible, were resected.

Supported by C.N.R. Grant No. 86.00724.44

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Introduction

Until the 1970s the classic therapy for osteogenic sarcomas of extremities was amputation or disarticulation[1-3] without any further treatment, but the results were so poor in terms of disease-free period and overall survival that clinicians directed their efforts to get a better prognosis.

The addition of adjuvant chemotherapy[2-7] obtained a significant decrease of the incidence of local relapse and distant metastases so that the following step was to apply this procedure in the preoperative period[8-12] in order to obtain a major necrosis of the primary[36] and a sort of prophylaxis of distant metastases clinically undetectable.

Even in this case the results were really encouraging because the percentage of limb salvage with this procedure reached 50–60%.[13-16]

In order to increase the percentage of resectable tumor, considering the good results observed with intra-arterial infusions, we thought to add to the advantage of a preoperative infusion and systemic chemotherapy the ones obtained by an hyperthermic antiblastic perfusion (HAP).

This procedure, employed since the 1960s in the therapy of in transit metastases with excellent results, presents the following advantages: 1) hyperthermia,[17-22] 2) intra-arterial administration of high doses of drugs, 3) synergistic effects between heat and drug,[23-29] and 4) mild toxicity, tolerable by all.

On this basis we decided upon the goal of obtaining a direct administration in the tumor's compartment of a high dosage of CDDP,[30] the most effective drug for osteogenic sarcoma,[31-33] whose effects are potentiated if given intra-arterially[20,34,35] or in perfusion.

Patients and Methods

From August 1983 to September 1986, 17 patients affected by osteogenic sarcoma of the extremities were admitted to our department. Local extension of the primary tumor left the orthopedic surgeon with only the posssibility of an amputation or disarticulation (Figures 1 and 7).

Table 1 shows the patients' characteristics while the characteristics of the tumors are summarized in Table 2. Table 3 shows the staging of patients at the admission, during the treatment and in the follow-up period. All the patients before treatment were biopsied to confirm the diagnosis. The usual work-up before treatment includes standard X-ray of the primary, chest X-ray, lung tomography, arteriography, CAT scan, NMR and radioisotopic scan (Figures 2, 3, 8 and 9). The planned treatment schedule was: 2 subsequent cycles of systemic administration of high dose MTX[a] (7.5 gr/M^2 BSA) associated with intra-arterial CDDP[b] for three days (40 mg/M^2 BSA each day) followed by HAP with high dose CDDP (200 mg/M^2 BSA for upper extremities, 300 mg/M^2 BSA for lower extremities).

HAP patients were submitted to two additional cycles of systemic high dose MTX + CDDP and in the first 10 cases to radiotherapy on the primary (3600 Rads total dose). Radiotherapy was abandoned for the technical difficulties that the orthopedic surgeon found at the time of the possible resection and because comparing the 2 series of patients that had or had not radiotherapy, we observed that there was not any difference in terms of necrosis of the primary or in terms of metastatic spread to the lung. On this basis we decided to omit radiotherapy because it did not seem to be helpful in these patients. Table 4 summarized times and steps of this treatment schedule.

During the infusion treatment, that usually takes 8 days for a cycle, patients were maintained in forced diuresis, for avoiding side effects such as nephrotoxicity from CDDP, and treated with Leucoverin[c] for preventing bone marrow depletion from MTX. At the end of the second cycles of infusion a needle biopsy for staging necrosis was carried out and then patients were submitted to HAP.[36]

Table 1
Patients

		Males	7
Patients	17		
		Females	10
Age Range	9–36		
Follow-up	6–42 Months	(Median 22 months)	

Table 2
Neoplasm's Characteristics

Distal Femur		5
Proximal Femur Neck		2
Diafisar Femur		5
Proximal Tibia		1
Proximal Humerus		4
Pathological Fracture		5
Medullar Duct Invasion		16
Radiological Diameter		5–27 cm.
Osteogenic Sarcoma	Chondroblastic	1
"	Osteoblastic	5
"	Hemorrhagic	3
"	Parosteal	1
"	Fibroblastic	1
"	NAS	6

Table 3
Staging of Patients

Before Treatment

- Hematological Tests (in particular liver and kidney function)
- Chest X-ray
- X-ray of tumor
- Arteriography
- CAT Scan or NMR
- Radio-Isotopic Scan
- Biopsy

During Treatment

- Hematological Tests
- Chest X-ray (monthly)
- Needle-Biopsy (after II infusion and perfusion)
- CAT Scan and/or NMR (after perfusion)
- X-ray of Primary (monthly)

Follow-up

- Chest X-ray Quarterly—CAT Scan of Lung if needed
- X-ray of Site of Primary Quarterly

a Methotrexate, American Cynamid Company, Wayne, NJ 07470

b Platinex, Bristol Italiana, Latina Italia

c Lederfolin, American Cynamid Company, Wayne, NJ 07470

Table 4

Treatment Schedule

Infusion

DAY 1 ↓ — High dose Methotrexate i.v. 7.5 gr/M² BSA

DAY 6 7 8 ↓ ↓ ↓ — Intra-arterial Cis-Platinum 40 mg/M² BSA each day continuously

↓

2 Weeks

↓

Second Cycle of Infusion

3 Weeks

↓

Hyperthermic Antiblastic Perfusion for One-Hour At 40–41°C With High Dose CIS-Platinum (200 mg/M² BSA for upper extremities) (300 mg/M² BSA for lower extremities)

↓

3 Weeks

↓

2 Additional Cycles of Systemic Chemotherapy as Above

↓

1–8 Months Eventual Radiotherapy 3600 RAD.*

↓

Orthopedic Surgery

*Radiotherapy on the primary, after the first 10 cases, was left for technical difficulties for the orthopedic surgery

Table 5 and Figure 14 explain our perfusing system. The surgical approach is through an extraperitoneal approach with a vertical lower paramedian skin incision for cannulating the iliac external vessels; for the upper extremities the approach is a subclavicular incision and, through the fibers of the pectoralis major and disconnecting the pectoralis minor, the axillary vessels are reached.

The temperature of the extremity is continuously checked by thermistor-probes inserted at different levels. Control of leakage is obtained by an accurate isolation of vessels with the temporary closure of vessels tributory to parts other than the extremities and by a scanner placed over the heart of patient to check the eventual leakage of labelled-Albumine injected in our extracorporeal circuit.

When the desired temperature of 40–40.5°C in the extremity is reached, the CDDP is injected in the circuit and perfusion lasts 60 minutes from this moment. At the end the limb is washed with five liters of Ringer's lactate[d] in order to remove the residual drug. During the postoperative period patients are maintained in forced diuresis to prevent nephrotoxicity from CDDP and after 2–3 days are mobilized. After 8–10 days from HAP it is usually possible to discharge the patient. Further details of this procedure are described elsewhere.[37–43]

Table 5

Perfusion System

Priming

- Plasma Expander[e] (1000 ml.)
- Packed Red Blood Cells (1 unit)
- HCT 20%
- Heparin (8000 U.I./Liter)
- $NaHCO_3$ 1 meq/ml
- Lidocaine[f] 400 mg.
- Tobramicine[g] 100 mg.
- Flow 0.1–1 L/min.

Temperature Monitoring

Probes are inserted in:

1) Skin
2) Proximal Muscle
3) Distant Muscle
4) Tumor
5) Subcutaneous Tissue
6) Arterial Line
7) Venous Line

After perfusion, when it was possible, a further needle biopsy was carried out and then patients were submitted to two or three additional cycles of systemic high dose MTX + CDDP.

The median duration of this treatment schedule was 3 months; then, with a standard X-ray of the tumor, a chest X-ray, CAT scan and arteriography, if needed, of the extremities (Figure 11), we send the patients to the First Orthopedic University Clinic of the Rizzoli Institute of Bologna, for the eventual resection.

Results

From a clinical point of view, a regression of symptoms in term of pain was observed after the two cycles of infusion and even a macroscopic regression of the primary both radiologically and functionally.[44] In the same way after HAP we observed an impressive radiological rerrangement of bone with an evident recalcification as a sort of healing process (Figures 4–

d Ringer's Lactate, S.A.L.F. Laboratories, Bergamo, Italy
e Plasmagel, Roger Bellon, Neully sur Seine, France
f Xylocaina, Byk Gulden, Konstanz, West Germany
g Nebicina, Eli Lilly Company, Indianapolis, IN 46285

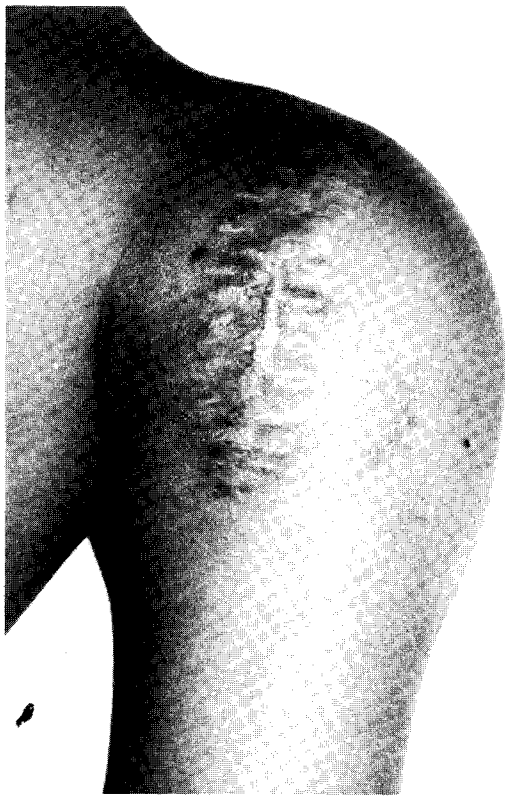

Figure 1: L.C. 9 years old with osteoblastic sarcoma of the left humerus before treatment.

Figure 2: L.C. X-ray showing the pathological fracture.

Figure 3: L.C. Arteriography before treatment.

Figure 4: L.C. After infusion + perfusion. It is evident that there are bone rearrangement and recalcification.

Figure 5: L.C. Pathological finding in which are shown the lines of section for evaluation of necrosis.

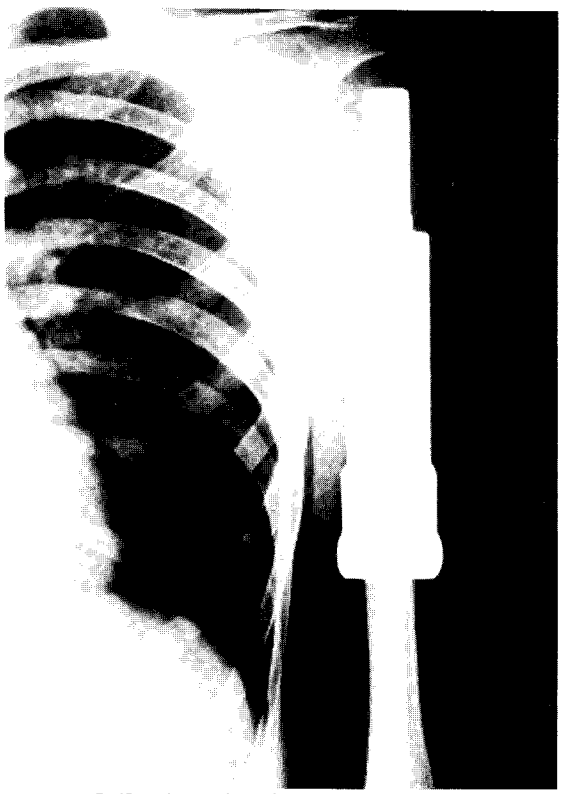

Figure 6: L.C. Final results after conservative resection plus endoprosthesis.

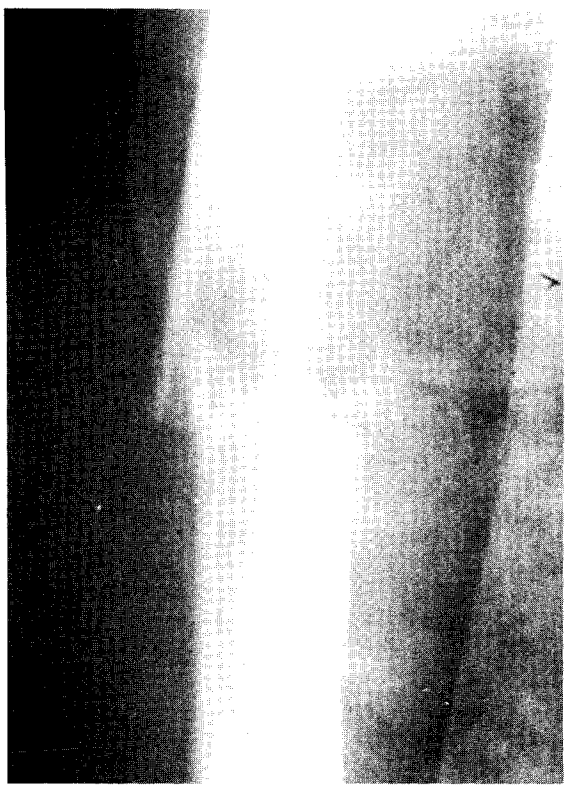

Figure 7: M.A. 15 years old with hemorragic osteogenic sarcoma of the femur with pathological fracture.

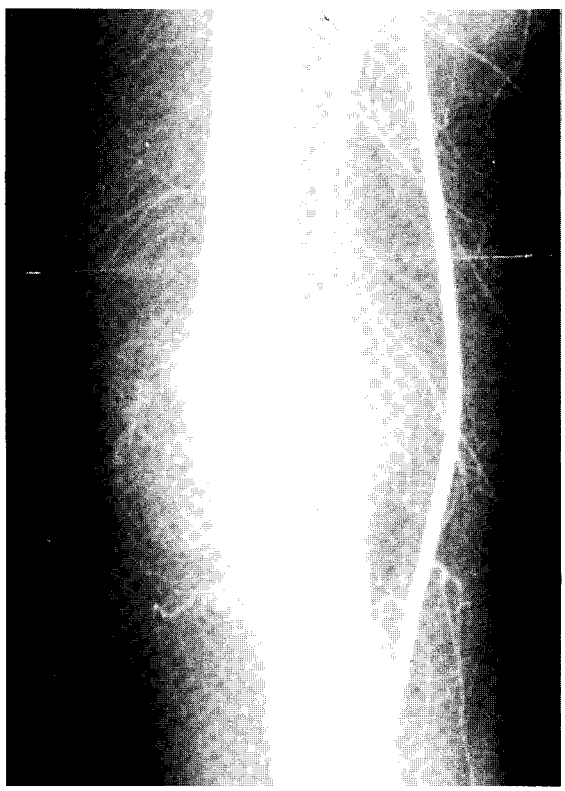

Figure 8: M.A. Arteriography before treatment.

Figure 9: M.A. CAT-scan showing the soft tissue invasion by neoplasm.

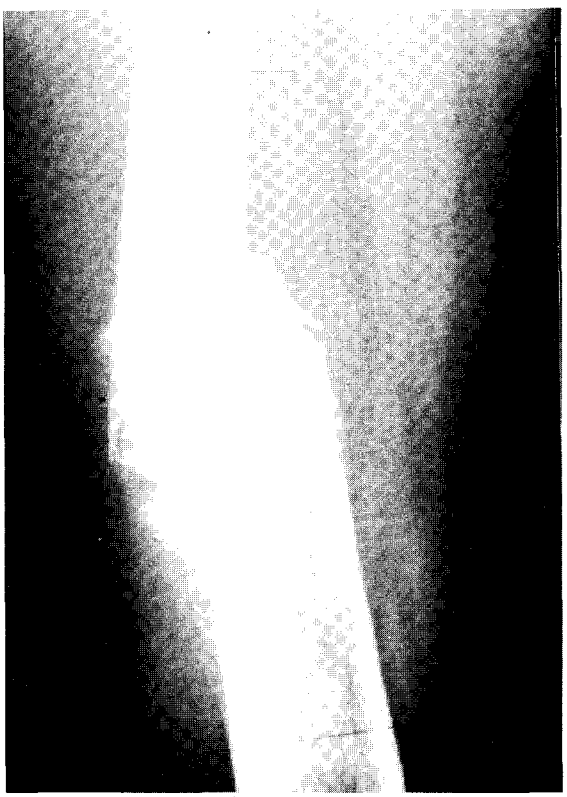

Figure 10: M.A. X-ray after infusion + perfusion, even in this case bone rearrangement and recalcification are evident.

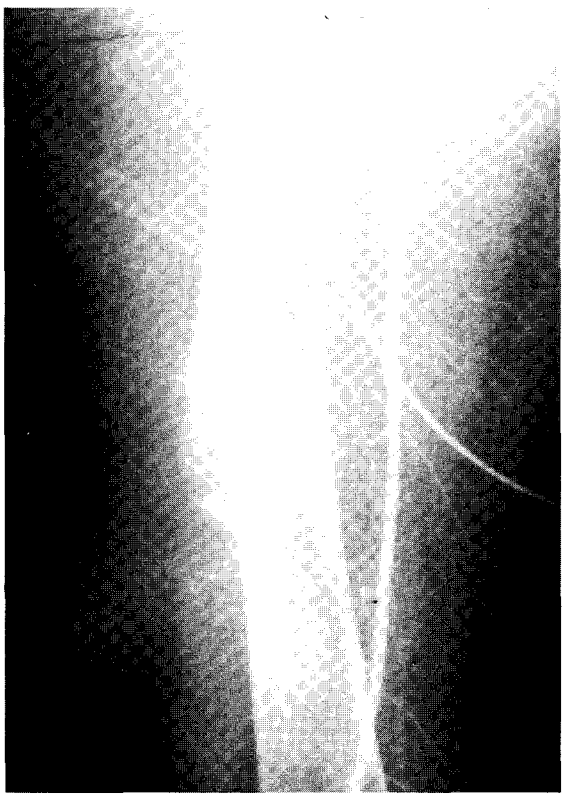

Figure 11: M.A. Arteriography after treatment.

Figure 12: M.A. Pathological finding.

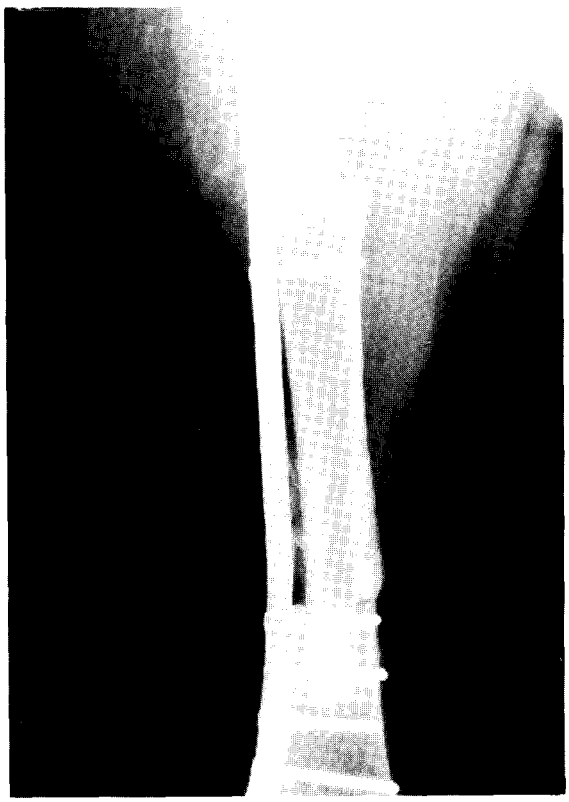

Figure 13: M.A. Final result after conservative resection with allograft.

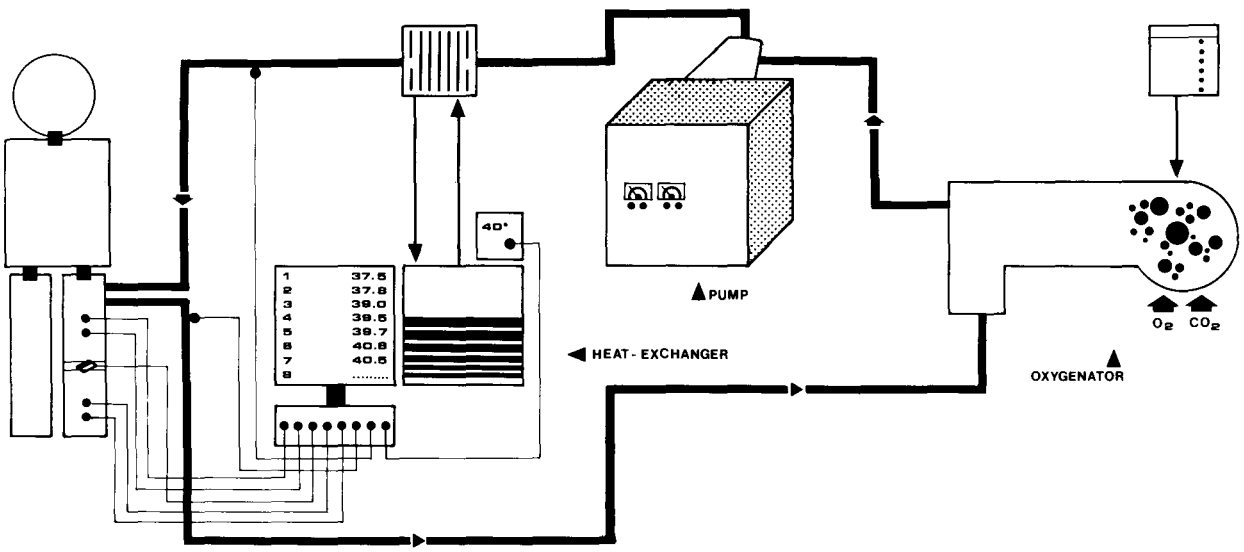

Figure 14: Design of our perfusion system.

10); the macroscopic regression and functional improvement were also increased by perfusion.

At the end of these long procedures the patients were completely re-evaluated. On the basis of these new evaluations, 10 patients were submitted to conservative radical treatment plus endoprosthesis, four were amputated for an insufficient regression or technical reasons, and in three patients no type of surgery was performed for the appearance of lung metastases in a short time after perfusion. Table 7 shows the results (Figures 6 and 13).

In regard to the evaluation of the grade of necrosis, the pathological findings are analyzed by serial sections using the classification[13,45,46,47] shown in Table 6. Table 8 shows the percentage of observed necrosis in 14 operated patients.

Out of the 5 patients with pathological fracture, three underwent en bloc resection plus endoprosthesis. None of the patients relapsed locally. Eight patients (Table 9) developed lung metastases with a time of appearance ranging from 2 to 15 months; of these, 5 were submitted to lung resection, but only in two cases was it radical, and 3 patients were not operable. In Table 10 is shown the final status of patients.

Table 6

Grading of Necrosis

Grade	I	= absence of necrosis
Grade	IIA	= < 50%
Grade	IIB	= > 50%
Grade	III	= minimal presence of tumor
Grade	IV	= no evidence of tumor

Table 7

Surgery

Conservative Treatment	10	59%
Amputation*	4	23%
Not Performed**	3	18%

*All for technical reasons, not for local progression
**For appearance of lung metastases in a short time after perfusion

Table 8

Evaluation of Necrosis

90–100%	8	47%
60–90%	4	23%
40–60%	1	6%
No Necrosis	1	6%
Not Resected	3*	17%

*For appearance of lung metastases in short time after perfusion

Table 9

Lung Metastases

		Radical Resection	2
Case	8 (47%)	Not Resected	3*
		Not Radical	3

Time of Appearance of Metastases after Perfusion = 2–15 Months

*3 cases in which primary was still present.

Table 10

Final Status

NED	11*	65%
AWD	4**	23%
DOD	2***	12%

*1 patient after lung resection
**2 patients without surgery of primary
***1 patient without surgery of primary

Complications

In regard to intra-arterial infusion and systemic chemotherapy, the treatment is uncomfortable from a symptomatological point of view because of the presence of nausea, vomiting and malaise. No major complication such as artritis, bleeding or infection related to the infusion procedure was observed. A transitory mild bone-marrow depletion, that was resolved spontaneously in a few days, was observed in all cases.

Perfusion treatment is generally well tolerated by patients; Table 11 summarized the complications: all patients showed an extensive edema of the extremities that was resolved in 2–3 weeks. A transitory bone-marrow depletion was observed in 5 patients, but even this resolved spontaneously in 5–10 days. No nephrotoxicity was evident and no amputation was successively carried out due to our perfusion treatment. In two cases there was a peripheral nervous deficit with subsequent foot drop, probably due to CDDP toxicity, that did not resolve.

Discussion

The number of patients involved and a brief follow-up do not allow any definite conclusions. However,

Table 11

Complications Due to Perfusion

Peripheral Nervous Deficit	2
Amputation (Due to Treatment)	0
Bone Marrow Depletion	5
Deep Phlebitis	2
Severe Transitory Edema	17
Nephrotoxicity	0
Wound Infections	1
Arterial Break	0
Hemothorax*	1

*Due to anticoagulants excess

some suggestive aspects must be stressed, especially if we consider that these series consist of patients for whom this procedure was the "the last step" before amputation.

Ten of 17 patients underwent conservative surgery because of the impressive reduction of the tumor mass and rearrangement of the bone and tumoral necrosis. Three of those 10 patients were affected by pathological fracture.

Even if the orthopedic surgeon were sometimes compelled to perform resection considered "marginal," this procedure can be viewed as a safe one. No local relapse was observed after a median follow-up of 22 months—which has to be judged a sufficiently long period for this disease.

Unfortunately, no modification in incidence of distance metastases was observed compared to other series.[13,14,15,48,49] But we are now evaluating the possibility of reducing this long period of treatment, as we cannot exclude that incidence of distant metastases must be correlated to the too long period during which the tumor continues to be vital.

Another consideration one may draw from these series is that this procedure is not practically useful in sarcoma of the femur neck, which cannot be sufficiently perfused, at least not by the use of our current technique. Conversely, no limitation exists for upper extremity tumors.

Again we emphasize the uselessness of radiotherapy on primary tumors, because no improvement was demonstrated when it was employed; indeed, it added many difficulties at the time of the eventual resection.

In conclusion, this treatment schedule showed quite good possibilities for local control of this disease, allowing a better quality of life for the patients. The HAP can play an important role in a multidisciplinary approach to the disease, especially when the problem of limb salvage is considered.

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Questions from the Audience

Question: Michael Hurdle, Indianapolis, IN: I am not but maybe should be familiar with the CIS-platinum. Is this a drug or technique appropriate or available in the United States at this point? Or is this more widely done in Europe?

Response: No. They allow it in the U.S. This procedure has not been employed. We are in touch with the North American perfusion group. We know they have some problem with the Food and Drug Administration for using CIS-platinum in the extracorporeal unit. But I think in a short time they will solve their problem. Now CIS-platinum is only allowed for safe use in systemic administration or at least interarterial.

Question: Do you all have experience also with the use of Malfolan and Nitrogen Mustard?

Response: Yes.We use Malfolan in the melenoma series. This drug was employed in the 1960s at the beginning of extracorporeal perfusion for all kinds of extremities, and with satisfactory results. But we are not encouraging everyone to use CIS-platinum for osteogenic sarcoma.