Pediatric & Adolescent Osteosarcoma ... progress from the past, prospects for the future

The Italian Rizzoli Experience
The Bone Tumor Center was established in 1955.

1,245 patients with non-metastatic osteosarcoma of the extremity between 1959 and 2006.
Prechemotherapy era

Chemotherapy era

Postchemotherapy era
Patients treated only with surgery

Between 1959 and 1970
127 patients
Amputation rate 90%
Cure rate 11%

Between 1971 to 1998
70 patients who refused chemotherapy
Amputation rate 78%
Cure rate 14%
(unpublished data)

Amputation according to the Cade method

Prophylactic irradiation of lungs

Immunotherapy with autologous vaccine

Amputation according to the Cade method
Radiotherapy at very high doses (10,000 rad)
If no metastases developed during the following 6 months, the patients underwent amputation.

16 patients
Metastases developed after 6 months in ten out of 16 patients, but an amputation was necessary anyway in 8 of them for the severe and painful local sequelae of the high dose radiotherapy.

Prophylactic irradiation of lungs
6 patients, only the right lung was treated at a dose of 1.5 Gy very early (from 2 to 5 months) metastases appeared in the irradiated lung.

**Immunotherapy with autologous vaccine**

16 patients
(amputation in 13 cases and limb salvage in 3)
The vaccine was obtained from resected tumor cells, previously irradiated with 12,000 rad

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**Surgery + autologous vaccine**
Cure rate 12%
Mean time to recurrence **16 months**
Mean survival time **26 months**.

**Surgery alone:**
Cure rate 11%
Mean time to recurrence **8 months**
Mean survival time **16 months**.

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Jaffe N. Favorable response of metastatic osteogenic sarcoma to pulse high-dose methotrexate with citrovorum rescue and radiation therapy. Cancer. 1973;31:1367-73
### Adjuvant Chemotherapy

#### Non-metastatic osteosarcoma of the extremity

223 patients with non-metastatic osteosarcoma of the extremity

<table>
<thead>
<tr>
<th>Period</th>
<th>Patients</th>
<th>Chemotherapy</th>
<th>%DFS</th>
<th>%Limb Salvage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972-1978</td>
<td>117</td>
<td>MTX-ADM-Vcr</td>
<td>45%</td>
<td>10%</td>
</tr>
<tr>
<td>1979-1983</td>
<td>106</td>
<td>LDMTX-ADM-Vcr vs MDMTX-ADM-Vcr</td>
<td>53%</td>
<td>22%</td>
</tr>
</tbody>
</table>


Improved prognosis thanks to chemotherapy

Increased percentage of long term survivors

Attention to patient’s quality of life

To reduce the rate of amputation + custom-made prosthesis

To start immediately with an effective systemic treatment

Bacci G. Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities. The Istituto Rizzoli Experience in 127 patients treated preoperatively with intravenous methotrexate (high versus moderate doses) and intraarterial cisplatin. Cancer, 1990, 1, 65, 2539-53.
12-year DFS was 46% (high dose methotrexate 52%, moderate dose 38%)

Resection rate 72%.

Non-metastatic osteosarcoma of the extremity

1986-1989

Neoadjuvant chemotherapy

Good responders  5-year DFS 67%,
Poor responder  5-year DFS 51 % (p=0.08)

10-year DFS 65% 10-year OS 74%

Recession rate 84%.

High cumulative dose of ADM (480 mg/m2)
4 cases of severe cardiotoxicity

Non-metastatic osteosarcoma of the extremity: results of a neoadjuvant chemotherapy protocol (IOR/OS-3) with high-dose methotrexate, intraarterial or intravenous cisplatin, doxorubicin, and salvage chemotherapy based on histologic tumor response. Tumori. 1999, 85, 458-64.
Non-metastatic osteosarcoma of the extremity: results of a neoadjuvant chemotherapy protocol (IOR/OS-3) with high-dose methotrexate, intraarterial or intravenous cisplatin, doxorubicin, and salvage chemotherapy based on histologic tumor response. Tumori. 1999, 85, 458-64.

Non-metastatic osteosarcoma of the extremity

1992

1993-1995

Resection rate 94%


In 1997 the Rizzoli Institute established the Italian Sarcoma Group (ISG), in order to promote a large Italian cooperation for the treatment of sarcoma patients.
<table>
<thead>
<tr>
<th>IOR/OS</th>
<th>Treatment Description</th>
<th>%DFS</th>
<th>%OS</th>
<th>%Resection</th>
</tr>
</thead>
</table>
| IOR/OS-1 | MTX-CDP-ADM-BCD  
Intermediate vs High dose MTX-  
Post operative chemo based on chemo-induced tumor necrosis No ADM in GR patients to MTX-CDP I.A | 46%  | 54%  | 72%        |
| IOR/OS-2 | MTX-CDP-ADM-(IFO in PR)  
Post operative chemo based on chemo-induced tumor necrosis IFO in PR patients to MTX-CDP IA-ADM | 65%  | 74%  | 84%        |
| IOR/OS-3 | MTX-CDP-ADM-(IFO in PR)  
I.A. vs I.V. CDP  
Post operative chemo based on chemo-induced tumor necrosis IFO in PR patients to MTX-CDP IA-ADM  
Reduced cumulative ADM dose, shorter treatment | 53%  | 61%  | 79%        |
| IOR/OS-4 | MTX-CDP-ADM- IFO  
All patients receiving IFO since preoperative phase | 56%  | 64%  | 94%        |
| ISG/SSG 1| MTX-CDP-ADM-high dose IFO  
Reduced cumulative ADM dose  
High dose Ifosfamide | 64%  | 77%  | 94%        |