Adjuvant chemotherapy for non-metastatic osteosarcoma of the extremity: a preliminary report.

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Nine cases seven males and two females of non-metastatic osteosarcoma of the extremity were treated with chemotherapy in an adjuvant fashion. The primary lesion was in the distal femur in five patients, the proximal tibia in two, and one each in the distal tibia and proximal femur. Pre-operative chemotherapy with intra-arterial cisplatin (100 mg/m²) and intravenous doxorubicin (60 mg/m²) was administered in two patients. Post-operatively, cisplatin (100 mg/m²) and doxorubicin (60 mg/m²) were given intravenously for one year. Doxorubicin was given until the dose reached a total of 450 mg/m². Surgery consisted of limb-sparing surgery in four of the cases, above-knee amputation in three, and one each of hip-disarticulation and below-knee amputation. Four of the nine patients were disease-free past 24 months. The two-year disease-free survival rate was 50.1% and overall survival was 87.5%. Refinements in treatment and more thorough pre-treatment investigations are discussed.

Key words: Chemotherapy, radiotherapy, adjuvant, osteosarcoma, extremity

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รายงานผู้ป่วยมะเร็งกระดูก ชนิด osteosarcoma ที่ยังไม่ได้กระจายไปที่อื่น 9 ราย ซึ่งได้รับการรักษาเสริมด้วยเคมีบำบัด ผู้ชาย 7 ราย ผู้หญิง 2 ราย มะเร็งเป็นที่ distal femur 5 ราย proximal tibia 2 ราย distal tibia และ proximal femur อย่างละ 1 ราย เคมีบำบัดก่อนผ่าตัดประกอบด้วย intra arterial cisplatin (100 mg/m²) และ doxorubicin (60 mg/m²) หลังผ่าตัดผู้ป่วยได้รับ cisplatin 100 mg/m² และ doxorubicin 60 mg/m² เป็นเวลา 1 ปี สำหรับขนาดยา doxorubicin อยู่ในช่วง 50 mg/m² ผลการรักษาเป็นที่มาของ อัตราผลสำเร็จในระยะ 2 ปี = 50.1% อัตราการยุติการใช้ในระยะ 2 ปี = 87.5% ถึงแม้การกลับเป็นใหม่จะต้องห่างนั้นเติมและการกระจายไปต่อ ยังเป็นสาเหตุสำคัญที่ทำให้ผู้ป่วยเสียชีวิตรักษาสามารถมีความปรับสภาพและอยู่ในระหว่างช่วงที่单身การใช้เคมีบำบัดเพื่อรักษาเสริมในโรค

อย่างไรก็ตาม ผู้รายงานเห็นว่ามีการทำงานรับรองช่องทางของยาเคมีที่ทำให้ผู้ป่วยการผ่าตัดรักษาเสริม ผู้ป่วยมีความรู้สึกและการใช้เคมีบำบัดที่มีความตรวจหายระยะของโรค โดยเฉพาะที่ผ่าน
Major advances in the management of non-metastatic osteosarcoma of the extremity have been made during the past 15 years. Adjvant chemotherapy has been shown to improve the disease-free survival rate.\(^{(1,3)}\) The rationale of pre-operative intra-arterial infusion of chemotherapy is that it facilitates limb-sparing surgery.\(^{(4,5)}\) Pulmonary resection of lung metastases has been the practice in many centers and shown to improve survival.\(^{(6,7)}\) Prophylactic whole lung irradiation has been carried out by many authors and the results have been encouraging.\(^{(8,9)}\)

We are reporting the preliminary results of disease-free and overall survival in treating with adjunctive chemotherapy nine patients who had non-metastatic osteosarcoma of the extremity.

**Material and methods.**

From January 1986 through December 1989, nine cases of non-metastatic osteosarcoma of the extremity were referred to the Department of Radiology, Faculty of Medicine, Chulalongkorn University for adjunctive chemotherapy. After the diagnosis had been confirmed by biopsy, evaluation for metastases was performed. All patients had a chest x-ray to rule out lung metastases. Radionuclide bone scan was done in cases in whom bone metastases had been suspected. Routine blood tests, including completed blood count, blood urea nitrogen, creatinine, liver function, electrolytes, uric acid, calcium, phosphate and magnesium, were obtained prior to administration of each cycle of chemotherapy. Electrocardiogram and left ventricular ejection fraction study were used to assess cardiac function. Computerized tomography (CT) of the lung was not used routinely to evaluate lung metastases. There were 7 males and 2 females. The primary tumor affected the right extremity in 6 patients and the left in 3 patients. The femur was affected in 6 patients and the tibia in 3 patients. The distal femur was the most common site of the primary, affecting 5 cases. The next sites of the primary tumor were: upper tibia (2 patients), upper femur (1 patient), and lower tibia (1 patient). Our adjunctive chemotherapy program consisted of pre or post-operative administration of cisplatin (Platinol; Bristol-Myers Oncology, New York, New York, U.S.A.) and doxorubicin hydrochloride (Adriblastina; Farmitalia Carlo Erba S.P.A., Montedison Group, Italy). Patients destined for limb-sparing surgery received pre-operative chemotherapy which consisted of intra-arterial infusion of cisplatin and intra-venous doxorubicin. Intravenous doxorubicin was given in dosages of 60 mg/m\(^2\) on the first day, escalating to 75 mg/m\(^2\) on the subsequent courses. Intra-arterial cisplatin was administered in dosages of 100 mg/m\(^2\) on the second day with prior hydration according to the regimen by Jaffe.\(^{(10)}\)

It was intended that the total number of courses of pre-operative chemotherapy would be four courses. Patients responding to pre-operative chemotherapy (criteria of response will be defined later) were scheduled to receive the same chemotherapy (cisplatin and doxorubicin intravenously) post-operatively for one year, omitting doxorubicin after the patient had attained 450 mg/m\(^2\). If response to pre-operative chemotherapy was sub-optimal, Ifosfamide (Holoxan; Asta-Werke, Degussa Pharma Gruppe, Germany), in dosages of 50-60 mg/Kg/day intravenously for five days with mesna protection, was given post-operatively for one year. For patients having immediate radical surgery, intravenous doxorubicin 60 mg/m\(^2\) on day 1 and cisplatin 100 mg/m\(^2\) on day 2 with prior hydration were given for on year. The doses of doxorubicin and cisplatin were escalated to 75 mg/m\(^2\) and 120 mg/m\(^2\), respectively, on subsequent courses. After having received a total of 450 mg/m\(^2\) of doxorubicin, it was dropped from the schedule and cisplatin alone was given for the rest of the therapy. Either pre-or post-operative chemotherapy was given every 3-4 weeks (Table 1,2).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Daily dose mg/m(^2)</th>
<th>Administration route</th>
<th>Administration on day</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>100</td>
<td>IA</td>
<td>1</td>
<td>Recycle</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>60-75</td>
<td>IV</td>
<td>1</td>
<td>every 4 weeks</td>
</tr>
</tbody>
</table>
Table 2. Post-operative chemotherapy.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Daily dose mg/m²</th>
<th>Administration route</th>
<th>Administration on day</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
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<td>IV</td>
<td>1</td>
<td>every 4 weeks</td>
</tr>
</tbody>
</table>

Arterial catheterization for infusion of cisplatin was performed under local anesthesia by the Seldinger technique. The cisplatin was infused intra-arterially for 2-4 hours. Metoclopramide was given intravenously for nausea and vomiting.

Two patients received CONPADRI-1.

Limb-sparing surgery was performed by local excision of the tumor, with generous margin, and replacement with bone graft or endoprosthesi.

Four patients (No. 3, 4, 6, 8) had limb-sparing surgery. Two (No. 3, 8) of these four patients had prior intra-arterial infusion of cisplatin before limb-sparing surgery. Three patients (No. 5, 7, 9) with distal femur tumor underwent above-knee amputation. There was a single patient (No. 1) with distal femur tumor who had hip disarticulation. Below-knee amputation was performed in only one patient (No. 2) with distal tibia tumor.

Prophylactic lung irradiation was given in only one patient (No. 7). She refused further irradiation after attaining a midlung dose of 750 cGy/1 week. Pre-operative irradiation to the primary was administered in one patient (No. 9).

Assessment of response to pre-operative chemotherapy was determined by changes in clinical symptoms, percentage of pathological tumor necrosis, or by resolution of tumor vascularity angiographically. Changes in clinical symptoms were evaluated by diminishing pain or regression in tumor size. Angiographic response was determined by the disappearance of tumor vascularity and tumor stain, or a total disappearance of tumor vascularity with slight persistence of capillary stain. Pathological tumor necrosis greater than 90% was considered a good response to intra-arterial chemotherapy.

Relapse was defined as a recurrence of tumor at any site. Local recurrence and distant metastases were defined, respectively, as recurrence of tumor at the primary site and at sites other than the primary one.

Toxicity was measured according to the World Health Organization (WHO) grading system.

The date of therapy initiation was used as the starting time for survival calculation. The study endpoints were disease-free survival and survival. The Kaplan Meier method was used for calculation of survival.

Results

Between January 1986 and December 1989, 15 patients with osteosarcoma of the extremity were registered for adjuvant chemotherapy. Of these, six were not eligible for the study due to distant metastases at presentation. Nine patients remained who could be studied. The minimal and maximal follow-up times were seven months and 80 months, respectively, with the median being 33 months.

The clinical data of the patients are shown in Table 3. The age of the patients ranged from 10 to 22 years, with the median age being 18 years. The most frequent presenting symptom duration of 1-6 months, the median being 3 months, and a history of mass or pain.

Of the two patients who had pre-operative intra-arterial infusion, one patient (No. 8) was considered to have "angiographic response" and tumor necrosis of over 90% after four courses of intra-arterial infusion of cisplatin. The other patient (No. 3) was operated on after having been given only one course of chemotherapy.

Local recurrence occurred in three patients (33.3%) and these recurrences occurred exclusively in the four patients who had undergone limb-sparing surgery. Pulmonary metastases were observed in five patients (55.6%), one of whom had malignant pleural effusion. One patient (No. 8) had both local and distant relapses.

At the time of data analysis (January 1993), six patients had died, three were alive : one with pulmonary metastases and two without disease. The two-year disease-free survival rate was 50.1%; overall survival was 87.5%.

Toxicity was mild. All patients had grade 1 hematotoxicity and grade 3 alopecia.
Table 3. Clinical data of the nine patients treated with adjuvant chemotherapy.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/Sex Year/Male or Female</th>
<th>Symptoms mass/pain (months)</th>
<th>Primary tumor site</th>
<th>Treatment modality</th>
<th>Surgery</th>
<th>Total dose dexamethasine (mg.)</th>
<th>Total dose cisplatin (mg.)</th>
<th>NED (months)</th>
<th>OS (months)</th>
<th>Current status</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>10/M</td>
<td>5</td>
<td>Left distal femur</td>
<td>S/C</td>
<td>Hip disarticulation</td>
<td>220</td>
<td>-</td>
<td>80+</td>
<td>80+</td>
<td>A/W</td>
<td>Received CONPADRI-1.</td>
</tr>
<tr>
<td>2.</td>
<td>21/M</td>
<td>6</td>
<td>Right distal tibia</td>
<td>S/C</td>
<td>BKA</td>
<td>440</td>
<td>22</td>
<td>22</td>
<td>33</td>
<td>Dead</td>
<td>Received CONPADRI-1.</td>
</tr>
<tr>
<td>3.</td>
<td>18/M</td>
<td>1</td>
<td>Right proximal tibia</td>
<td>A/S/C</td>
<td>L-S</td>
<td>600</td>
<td>600</td>
<td>14</td>
<td>30</td>
<td>Dead</td>
<td>Pulmonary metastasis 22 months following treatment.</td>
</tr>
<tr>
<td>4.</td>
<td>22/M</td>
<td>3</td>
<td>Right proximal tibia</td>
<td>S/C</td>
<td>L-S</td>
<td>550</td>
<td>850</td>
<td>7</td>
<td>7</td>
<td>Dead</td>
<td>Pulmonary metastasis 14 months following treatment.</td>
</tr>
<tr>
<td>5.</td>
<td>18/M</td>
<td>3</td>
<td>Right distal femur</td>
<td>S/C</td>
<td>AKA</td>
<td>440</td>
<td>900</td>
<td>13</td>
<td>15</td>
<td>Dead</td>
<td>He was a foreigner who was lost to follow-up after a local recurrence at 7 months (Assumed to have died.)</td>
</tr>
<tr>
<td>6.</td>
<td>16/F</td>
<td>5</td>
<td>Left proximal femur</td>
<td>S/C</td>
<td>L-S</td>
<td>960</td>
<td>1300</td>
<td>29</td>
<td>33</td>
<td>Dead</td>
<td>Pulmonary metastasis 15 months following treatment.</td>
</tr>
<tr>
<td>7.</td>
<td>19/F</td>
<td>3</td>
<td>Left distal femur</td>
<td>S/C</td>
<td>AKA</td>
<td>300</td>
<td>600</td>
<td>52+</td>
<td>52+</td>
<td>A/W</td>
<td>Local recurrence 29 months following treatment. She died from DVT.</td>
</tr>
<tr>
<td>8.</td>
<td>11/M</td>
<td>4</td>
<td>Right distal femur</td>
<td>A/S/C</td>
<td>L-S</td>
<td>630</td>
<td>650</td>
<td>30</td>
<td>45+</td>
<td>A/M</td>
<td>Refused further chemotherapy. Received whole lung irradiation 750 cGy/1 wk.</td>
</tr>
<tr>
<td>9.</td>
<td>10/M</td>
<td>1</td>
<td>Right distal femur</td>
<td>R/S/C</td>
<td>AKA</td>
<td>550</td>
<td>770</td>
<td>24</td>
<td>28</td>
<td>Dead</td>
<td>Local recurrence at 30 months and pulmonary metastasis at 34 months following treatment. 90+% tumor necrosis after IA CDDP. Radiation therapy pre-operatively of the primary (800 cGy/2 fractions) Malignant pleural effusion 24 months following treatments.</td>
</tr>
</tbody>
</table>

S = surgery; C= chemotherapy; a= intra-arterial chemotherapy; R= radiation therapy; A/W = alive and well; BKA = below knee-amputation; L-S = limb sparing surgery; AKA= above-knee amputation; DVT= deep vein thrombosis; A/M= alive with metastasis; CDDP= cisplatin
NED = no evidence of disease; OS= overall survival.

* Epirubicin.
Discussion

Cade, in 1955, reported a method of irradiation followed by delayed amputation if no pulmonary metastases had developed at six months. The method yielded a two-year survival rate of 20%.

Douglass and co-workers from Roswell Park Memorial Institute, reported, in 1975, a 12% five-year survival rate in patients with osteosarcoma treated with amputation alone. Between 1966 and 1972, other authors also reported a cure rate of 15-20%.

In the past several years major advances in incorporating adjuvant chemotherapy in the management of non-metastatic osteosarcoma of the extremity produced a two-year disease-free survival rate in excess of 50%. The most widely used chemotherapeutic agents are cisplatin, doxorubicin and high-dose methotrexate.

This study was undertaken to evaluate the effect of adjuvant chemotherapy on disease-free survival and overall survival. The two-year disease-free survival rate of our patients was 50.1%, overall survival was 87.5%. These results compare favorably with those of other reports and are better than that of our patient who underwent surgical treatment alone (2-year disease-free survival = 11.1%, overall survival = 22.2%). Before the widespread use of chemotherapy, the incidence of pulmonary metastases was at least 80%. This figure has dropped to 30-40% with the advent of adjuvant chemotherapy. Guilianono et al. reported an incidence of 47%. In this report the incidence of pulmonary metastases was 55.6%. This high incidence of pulmonary metastases, despite administration of adjuvant chemotherapy, could be due to two factors. Firstly, the pre-treatment evaluation of our patients did not include CT scan of the chest to rule out pulmonary metastases at presentation. The sensitivity of a standard chest x-ray was only 57%. Secondly, most of the patients received suboptimal doses of chemotherapy. Drug dose intensity has been reported to be an important determinant of prognosis.

Local recurrence was also a major cause of failure. It is interesting to note that all the local recurrences occurred in patients who had limb-sparing surgery. Although an attractive procedure sparing the young patient an amputation, limb-sparing surgery has still to be refined, possibly by incorporating radiation of the primary tumor prior to surgery in order to reduce local recurrence.

Conclusion

Our experience in treating with adjuvant chemotherapy a small number of patients having osteosarcoma of the extremity compares favorably with that of other reports in the literature. We achieved a two year disease-free survival rate of 50.1% and overall survival of 87.5%. Although pulmonary metastases and local recurrence are still the major causes of failure, our results support the use of adjuvant chemotherapy for patients presenting with non-metastatic osteosarcoma of the extremity. Long-term results are awaited. Refinements in treatment have to be made in order to reduce the aforementioned types of failure. In our subsequent trial, pre-operative staging with CT scan of the lung, optimal dosages of chemotherapy and prophylactic lung irradiation will be incorporated in our treatment program.

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