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Activity of Intraarterial Carboplatin as a Single Agent in the Treatment of Newly Diagnosed Extremity Osteosarcoma

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Background. Chemotherapy has dramatically improved the rates of cure and survival of patients with localized and metastatic osteosarcoma. Nonetheless, the number of chemotherapeutic agents active against osteosarcoma is limited to doxorubicin, cisplatin, high-dose methotrexate, and ifosfamide. Carboplatin, a cisplatin analogue, has been tested as a single agent in patients with recurrent osteosarcoma or as part of multiagent chemotherapy in newly diagnosed patients. ***Procedure.*** We tested the activity and toxicity of two cycles of intraarterial carboplatin as a "window therapy" (600 mg/m^2 per cycle) in 33 consecutive patients with extremity osteosarcoma before the start of multiagent chemotherapy. Response was based on clinical (tumor diameter, local inflammatory signs, and range of motion) and radiological parameters (plain local films and arteriographic studies prior to drug administration). ***Results.*** Patients' age ranged between 8 and 18 years (median age 13 years). Primarytumor originated from the femur (15 patients), tibia (10 patients), fibula (4 patients), humerus (3 patients), and calcaneus (1 patient). Only 7 patients (21%) had metastatic disease at diagnosis (5 in the lung and 2 in other bones). A favorable clinical and radiological response was documented in 81% and 73% of the patients, respectively. Clinical and radiological progression occurred in 12% and 9% of the patients, respectively. Seventeen of the patients remain alive and disease-free. Survival and event-free survival at 3 years for nonmetastatic patients are 71% (SE = 9%) and 65% (SE = 9%), respectively; for metastatic patients, the figures are 17% (SE = 15%) and 14% (SE = 13%), respectively. ***Conclusions.*** We conclude that carboplatin is an active agent in the treatment of newly diagnosed extremity osteosarcoma. Med. Pediatr. Oncol. 33:71–75, 1999. © 1999 Wiley-Liss, Inc.

Key words: osteosarcoma; extremity tumors; carboplatin (CBDCA); childhood cancer; adolescents

INTRODUCTION

Adjuvant chemotherapy is beneficial in the treatment of both localized and metastatic osteosarcoma of the extremity [1,2]. Neoadjuvant chemotherapy (preoperative chemotherapy) has been employed in addition to adjuvant chemotherapy in the treatment of osteosarcoma. No randomized study has yet shown the superiority of this combination over adjuvant chemotherapy alone [3].

Three clear advantages result from the use of neoadjuvant chemotherapy. First, it makes more patients eligible to undergo limb-sparing procedures, leading to significant gain in function of the affected limb in some of these patients. Second, the degree of tumoral destruction found in the pathological specimen after neoadjuvant chemotherapy may help in the choice of further treatment; patients considered to have a poor response could have alternative drugs used in the adjuvant setting [4]. Finally, neoadjuvant chemotherapy leads to prompt treatment not only of local but also of metastatic disease. Besides its therapeutic advantages, neoadjuvant chemo-

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therapy is an effective and elegant means of testing tumoral response to new drugs.

Carboplatin (CBDCA), a platinum-derived agent, has some overlapping antitumoral activity with cisplatinum and has been tested in the treatment of several pediatric solid tumors [5–8]. The use of CBDCA instead of cisplatin would be rather attractive, considering that it is better tolerated owing to easier administration and lack of severe emesis, ototoxicity, and nephrotoxicity.

Cisplatin is one of the most important agents in the treatment of osteosarcoma [9–12]. CBDCA has been tested as a single agent in the treatment of recurrent or refractory osteosarcoma [13–17] and as part of multiagent chemotherapy in newly diagnosed patients [18], but the experience with CBDCA as a single agent in newly diagnosed osteosarcoma patients is still scant [19]. We describe clinical and radiographic initial responses and toxicity in a group of newly diagnosed patients with extremity osteosarcoma receiving intraarterial CBDCA as a single agent.

MATERIALS AND METHODS

From October, 1991, to April, 1994, all patients with the diagnosis of high-grade osteosarcoma of an extremity were enrolled in a study employing intraarterial CBDCA as single agent in an experimental treatment (window therapy) as part of neoadjuvant chemotherapy. Patients with large tumors not deemed suitable for a limb-sparing operation went on to have local amputation; these patients were treated in the same chemotherapeutic study (Osteosarcoma study 3) but were excluded from this report because of their ineligibility to receive intraarterial CBDCA.

After the histological confirmation of a high-grade osteosarcoma, an initial workup consisted of complete history and physical examination, complete blood counts (CBC), and full biochemistry, including alkaline phosphatase, lactic dehydrogenase, and electrolytes. Normal renal (BUN, creatinine and creatinine clearance), hepatic (SGOT, SGPT, bilirubin, and coagulation profile), and cardiac function (echocardiogram and electrocardiogram) for age were required for study entry. Normal audiometric evaluation was also mandatory at diagnosis. Radiological evaluation at diagnosis consisted of plain chest (PA and lateral) and local films, computerized axial tomography (CAT scan) of the chest and a radioisotope bone scan. A CAT scan or magnetic resonance imaging (MRI) of the affected bone was obtained. These exams were then repeated after the end of the CBDCA window therapy in some patients and at regular intervals during and after the end of therapy. Also at diagnosis, an angiographic study of the local tumoral vasculature was performed prior to the administration of intraarterial chemotherapy. This exam was repeated again, once, 2 weeks later along with the second dose of CBDCA.

Clinical and Radiological Evaluation

Initial response to two cycles of intraarterial CBDCA was evaluated according to clinical and radiological parameters. Clinical responses were based on the following criteria: 1) serial measurements of the tumor diameter; 2) local pain and tenderness, edema, and temperature; and 3) range of motion of the affected limb. A favorable response (FR) was defined as when at least two of the criteria defined above were definitely improved without any sign of progression, and stable disease (SD) was defined as minimal or no change or improvement of only one of the criteria given above. The diagnosis of progressive disease required clear worsening of at least one of the criteria given above.

Radiologic responses were based on serial local films performed both at diagnosis and after completion of the window therapy and on two angiographic studies performed along with the two intraarterial infusions of CBDCA. The films were reviewed by a single radiologist (H.L.), unaware of the patients' clinical status. In the plain films, responses were evaluated based on changes in the size of the soft tissue involvement, aspect of the bone, alterations in intensity and pattern of calcification, and visualization of fat planes. A favorable response was documented whenever there was a combination of the following: a decrease in the soft tissue mass, an increase in bone density (evidence of new bone formation) and in periosteal reaction, an increase in calcification, and a better visualization of fat planes.

Angiography required the percutaneous insertion of a catheter through either the femoral or the brachial artery under fluoroscopic guidance. The tip of the catheter was then positioned into the appropriate artery supplying the neoplasm or, in cases when its determination was unclear, immediately proximal to the tumor. No angiographic study was performed at the end of the window therapy.

Evaluation was based on the caliber and/or number of vessels, tumor vascularity, and tumor stain. A favorable angiographic response was considered as reduction in caliber and/or number of vessels and/or diminution in neovascularity and/or tumor stain.

Treatment Protocol

Neoadjuvant chemotherapy consisted of two initial courses (window therapy) of intraarterial CBDCA given at a 2-week interval, followed by three courses of rotating pairs of drugs. CBDCA 600 mg/m^2 diluted in 500 cc of normal saline was infused intraarterially over 1 hr at week −4. A second intraarterial CBDCA dose was given two weeks later (week −2). Appropriate antiemetics and intravenous fluids were given on both occasions. At both

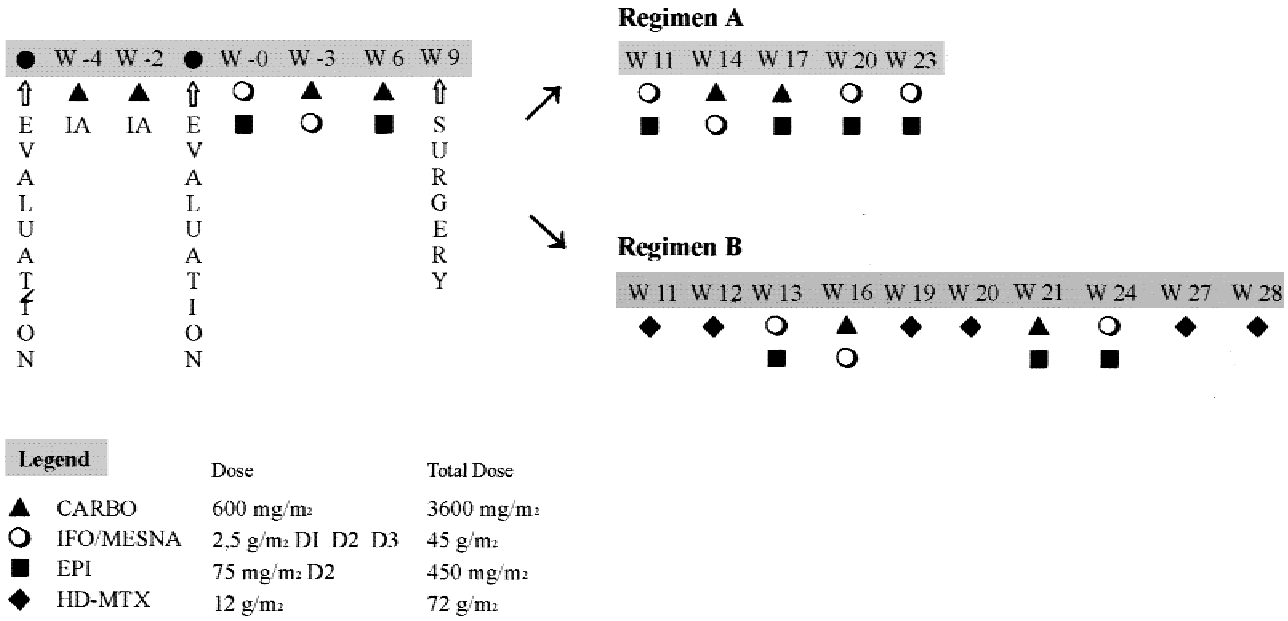

Fig. 1. Osteosarcoma study 3.

instances, a complete arteriography of the affected bone was obtained. Renal and hepatic functions were followed weekly, and a CBC was performed twice per week during the window therapy. Following the initial two courses of CBDCA, the patients received a combination of ifosfamide (IFO), CBDCA, and epirubicin (EPI) given as a two-drug pair (IFO/EPI, CBDCA/IFO, and CBDCA/EPI) at 3-week intervals for a total of 9 weeks. At week 9, patients underwent definitive surgery, either conservative or limb amputation, based on clinical and radiological response. Adjuvant chemotherapy for patients who had a limb-sparing procedure and initial tumor diameter <12 cm consisted of five additional two-drug pair courses of the same chemotherapeutic agents mentioned above (regimen A). For those patients who underwent amputation or had tumor diameter ≥12 cm at diagnosis, six cycles of high-dose methotrexate (12 g/m^2) followed by leucovorin rescue were added to the previously described treatment (regimen B). Treatment schema are shown in Figure 1.

No cytokines were used during either neoadjuvant or adjuvant chemotherapy. Toxicity to the two cycles of intraarterial chemotherapy was recorded and its interpretation was based on the National Cancer Institute common toxicity criteria. Informed consent was obtained from the patient's parents or guardians following institutional standards at the time of this study.

RESULTS

Thirty-three consecutive patients were enrolled in this study and received initial intraarterial CBDCA treatment. All patients are evaluable for toxicity and for clinical and radiological response. Patients' clinical characteristics are shown in Table I. There were 19 males (58%) and 14 females (42%), and their ages ranged from 8 to 18 years (median age 13 years); 57% of the patients were 15 years old or younger at the time of diagnosis. Primary tumors arise in the femur (15 patients), tibia (10 patients), fibula (4 patients), humerus (3 patients), and calcaneus (1 patient). Classification according to osteosarcoma subtype was as follows: osteoblastic (17 patients), chondroblastic (3 patients), fibroblastic (2 patients), telangiectatic (1 patient), and mixed osteoblastic/chondroblastic (1 patient); nine patients did not have their tumor subtype available. Twenty-six patients had nonmetastatic disease at diagnosis (79%), and, among the 7 with metastases detected, 5 had lung metastases and 2 metastases in other bones.

A favorable clinical response following the two initial cycles of intraarterial CBDCA was documented in 27 patients (81%), and 2 patients (6%) had stable disease; only 4 of 33 patients (12%) had progressive clinical disease after this initial chemotherapy. A favorable radiological response documented by imaging studies was confirmed in 73% of the patients; 18% had stable disease and 9% had radiographic tumoral progression after 2 cycles of intraarterial chemotherapy.

At week 9, 17 patients (51%) underwent conservative limb-sparing procedures and 11 (33%) had an amputation performed; 5 patients (15%) refused surgical treatment and eventually died of tumoral progression. Seventeen patients remain alive disease-free at the time of this report in July, 1998. The survival and event-free survival at 3 years for patients with nonmetastatic disease are 71% (SE = 9%) and 65% (SE = 9%), respectively; for metastatic patients they are 17% (SE = 15%) and 14% (SE =

TABLE I. Clinical Characteristics of the 33 Patients

	Patients (n)	Percentage
Sex		
Male	19	58
Female	14	42
Age		
<10 years	06	18
10–15 years	13	39
>15 years	14	43
Primary site		
Femur	15	46
Tibia	10	30
Fibula	04	12
Humerus	03	09
Calcaneus	01	03
Nonmetastatic	26	79
Metastatic		
Lung	05	15
Bone	02	06

13%), respectively. No complications were found after the 66 arterial punctures performed in these patients.

Toxicity

No toxic deaths occurred during the duration of this study. Myelosuppression was the most frequent side effect associated with intraarterial administration of CBDCA. Thrombocytopenia (platelets $\leq$50,000/μl), anemia (hemoglobin <8 g/dl), and neutropenia (granulocytes <1,000/μl) were observed in 12% (4/33), 15% (5/33), and 18% (6/33) of the patients during the two cycles of CBDCA, respectively. None of the patients developed a granulocyte count less than 500/μl, and no episodes of neutropenic fever occurred after CBDCA administration. Details of the hematological toxicity are shown in Table II.

No renal, hepatic, neurological, or gastrointestinal toxicity was observed. Sixteen patients had a complete audiologic evaluation before and after two cycles of intraarterial CBDCA. Thirteen patients had a normal audiologic evaluation in both instances. Two asymptomatic patients had a moderate high-frequency hearing loss (range between 6,000 and 8,000 Hz) after CBDCA treatment. One patient had a severe hearing loss before treatment start that remained unchanged after CBDCA treatment.

DISCUSSION

We observed a satisfactory response to CBDCA used as a single agent in an up-front window treatment in newly diagnosed patients with metastatic and nonmetastatic extremity osteosarcoma. This response was based on clinical and radiological evaluation.

Few studies so far have investigated CBDCA as a single agent in the treatment of osteosarcoma. Three early phase I studies evaluated 17 patients with osteosarcoma, obtaining complete responses in 2 and stable disease in 6 patients [13–15]. Tan et al. (personal communication) reported a study using intravenous CBDCA in 16 previously treated patients with osteosarcoma; 2 patients had stable disease lasting 2 and 5 months. Bieling et al. (personal communication) treated 20 patients with recurrent or refractory metastatic osteosarcoma with intravenous CBDCA. Radiological responses consisted of only one patient with minimal tumoral decrease (between 10% and 50%) and 2 patients with stable disease. Lewis et al. [16] treated 10 patients with recurrent or refractory osteosarcoma with intravenous CBDCA; among the 9 evaluable patients, only 3 patients had stable disease. No radiological responses were seen. Ettinger et al. [17] treated 14 patients with recurrent osteosarcoma with intravenous CBDCA; among the 12 evaluable patients with osteosarcoma, none had any objective response to treatment. Myelosuppression (thrombocytopenia and neutropenia) was the most prominent side effect attributable to CBDCA in the above-mentioned studies. Ototoxicity, nephrotoxicity, nausea and vomiting, increase in liver enzymes, hypomagnesemia, and seizures were also observed more rarely.

TABLE II. Hematologic Toxicity According to the Carboplatin Cumulative Dose

	Cumulative dose (%)	
Parameter	600 mg/m^2	1,200 mg/m^2
Hemoglobin		
<10 g/dl	7/33 (21)	9/33 (27)
<8 g/dl	2/33 (6)	5/33 (15)
White cell count		
<3,000/mm^3	0%	6/33 (18)
<1,000/mm^3	0%	0%
Neutrophils		
<1,000/mm^3	0%	6/33 (18)
<500/mm^3	0%	0%
Platelet count		
<100,000/mm^3	1/33 (3)	8/33 (24)
<50,000/mm^3	0%	4/33 (12)

In the only other study using CBDCA in newly diagnosed patients, Ferguson et al. [19] described the response to two courses of CBDCA administered as a continuous intravenous infusion (1,000 mg/m^2 per cycle) among 37 patients with previously untreated metastatic or unresectable osteosarcoma. Following radiographic or pathologic criteria (disappearance of pulmonary metastases, more than 50% decrease in primary tumor and more than 90% nonviable tumor in the pathologic specimen), 8 of 34 (23%) of the evaluable patients showed response at one or more individual sites; considering all sites of disease, only one patient had a partial response to this treatment. Myelosuppression, including both neutropenia and thrombocytopenia, was a significant side effect with frequent delays in chemotherapy.

Our results and those described above differ markedly. First, when testing a chemotherapeutic agent in

heavily pretreated patients, most of whom had already received cisplatin, there is a considerable chance that these tumors have already developed multidrug resistance and, therefore, show a poor response to therapy. Second, comparing our study to that of Ferguson et al. [19] with nonpreviously treated patients, we included a higher percentage of good prognosis patients. Almost 80% of our patients had localized, nonmetastatic osteosarcoma and about 64% (18/28) had tumor dimensions <12 cm. Third, we applied different criteria to define response, which may account for part of the marked difference in results between the two studies.

It is also important to emphasize that treatment was well tolerated. Myelosuppression, although present, was not severe and did not cause delays in the therapy at the schedule and doses employed in this study. No nephrotoxicity or ototoxicity was seen among the patients treated.

One of the main deficiencies in this study is the lack of correlation between radiological and pathologic findings by the end of the window therapy. Pathologic response based on the extent of tumor cell necrosis and fibrovascular proliferation is the gold standard form of evaluating tumoral response to neoadjuvant chemotherapy in the treatment of osteosarcoma. However, we could not justify submitting the patients to a surgical procedure after only two cycles of CBDCA and prior to receiving the benefit of proven multiagent chemotherapy. A third angiography was not performed either, because the open front window consisted of only two doses of intraarterial CBDCA. We concluded from our study that intraarterial CBDCA is active in the treatment of osteosarcoma and should be tested in combination with other proven chemotherapy agents in patients with this malignancy.

CONCLUSIONS

We believe that the results shown in this study are appealing. The therapy was given in an outpatient clinic and was well tolerated. Considering that hospitalization of patients to receive cisplatin increases considerably the cost of treatment, there is an obvious benefit to be derived from using CBDCA. Besides, it would be difficult nowadays to reproduce this treatment strategy employing CBDCA as a single agent, as opposed to CBDCA as part of a multidrug chemotherapy, in patients with good-prognosis extremity osteosarcoma. We conclude that CBDCA is an active agent in the treatment of osteosarcoma and that it should be incorporated into combination chemotherapy regimens to be tested in large trials.

REFERENCES

1. Link MP, Goorin AM, Miser AW, et al. The effect of adjuvant chemotherapy on relapse-free survival in patients with osteosarcoma of the extremity. N Engl J Med 1986;314:1600–1606.
2. Bacci G, Mercuri M, Briccoli A, et al. Osteogenic sarcoma of the extremity with detectable lung metastases at presentation. Results of treatment of 23 patients with chemotherapy followed by simultaneous resection of primary and metastatic lesions. Cancer 1997; 79:245–254.
3. Goorin A, Baker A, Gieser P, et al. No evidence for improved event free survival (EFS) with presurgical chemotherapy (PRE) for non-metastatic extremity osteogenic sarcoma (OGS): Preliminary results of a randomized Pediatric Oncology Group (POG) trial 8651 (abstract). Proc Am Soc Clin Oncol 1995;14:444.
4. Rosen G, Caparros B, Huvos AG, et al. Preoperative chemotherapy for osteogenic sarcoma: Selection of postoperative adjuvant chemotherapy based on the response of the primary tumor to preoperative chemotherapy. Cancer 1982;49:1221–1230.
5. Heideman RL, Kovnar EK, Kellie SJ, et al. Preirradiation chemotherapy with carboplatin and etoposide in newly diagnosed embryonic pediatric CNS tumors. J Clin Oncol 1995;13:2247–2254.
6. Zoubek A, Kajtar P, Flucher-Wolfram B, et al. Response of untreated stage IV Wilms' tumor to single dose carboplatin assessed by "up front" window therapy. Med Pediatr Oncol 1995;25:8–11.
7. Frascella E, Pritchard-Jones K, Modak S, et al. Response of previously untreated metastatic rhabdomyosarcoma to combination chemotherapy with carboplatin, epirubicin and vincristine. Eur J Cancer 1996;32A:821–825.
8. Alvarado CS, Kretschmar C, Joshi VV, et al. Chemotherapy for patients with recurrent or refractory neuroblastoma: A POG phase II study. J Pediatr Hematol Oncol 1997;19:62–67.
9. Jaffe N, Knapp J, Chuang VP, et al. Osteosarcoma: Intra-arterial treatment of the primary tumor with cis-diammine-dichloroplatinum II (CDP). Angiographic, pathologic and pharmacologic studies. Cancer 1983;51:402–407.
10. Jaffe N, Raymond AK, Ayala A, et al. Effect of cumulative courses of intra-arterial cis-diamminedichloroplatin-II on the primary tumor in osteosarcoma. Cancer 1989;63:63–67.
11. Jaffe N, Smith D, Jaffe MR, et al. Intraarterial cisplatin in the management of stage IIB osteosarcoma in the pediatric and adolescent age group. Clin Orthop 1991;270:15–21.
12. Petrilli AS, Gentil FC, Epelman S, et al. Increased survival, limb preservation, and prognostic factors for osteosarcoma. Cancer 1991;68:733–737.
13. Foster BJ, Clagett-Carr K, Leyland-Jones B, Hoth D. Results of NCI-sponsored phase I trials with carboplatin. Cancer Treat Rev 1985;12(Suppl A):43–49.
14. Bacha DM, Caparros-Sison B, Allen JA, et al. Phase I study of carboplatin (CBDCA) in children with cancer. Cancer Treat Rep 1986;70:865–869.
15. Gaynon PS, Ettinger LJ, Moel D, et al. Pediatric phase I trial of carboplatin: A Childrens Cancer Study Group report. Cancer Treat Rep 1987;71:1039–1042.
16. Lewis IJ, Stevens MCG, Pearson A, et al. Phase II study of carboplatin in children's tumours (abstract). Proc Am Soc Clin Oncol 1993;12:412.
17. Ettinger LJ, Gaynon PS, Krailo MD, et al. A phase II study of carboplatin in children with recurrent or progressive solid tumors. A report from the Childrens Cancer Group. Cancer 1994;73:1297–1301.
18. Meyer WH, Pratt CB, Rao BN, et al. Curative therapy for osteosarcoma without cisplatin—Preliminary results of SJCRH OS-91 (abstract). Proc Am Soc Clin Oncol 1997;16:512a.
19. Ferguson W, Harris M, Link M, et al. Carboplatin in the treatment of newly-diagnosed metastatic or unresectable osteosarcoma: A Pediatric Oncology Group study (abstract). Proc Am Soc Clin Oncol 1996;15:521.