Small Cell Osteosarcoma Successfully Treated by High-dose Ifosfamide and Methotrexate, Combined with Carboplatin and Pirarubicin

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Abstract. Small cell osteosarcoma (SCO) is the most rare subtype of osteosarcoma and has a poor prognosis. An 11-year-old boy presented with a 2-month history of painful tumefaction in the lower leg. Imaging analysis demonstrated a mixture of osteolytic and osteosclerotic lesions in the proximal tibia and extraskeletal area. Histology of the open biopsy showed small round cells producing mucous matrix. Based on these findings, SCO was suspected. The patient received three cycles of neoadjuvant chemotherapy using high-dose ifosfamide, high-dose methotrexate, pirarubicin and carboplatin. Wide-margin resection was performed followed by tibial lengthening using the Ilizarov method and two cycles of adjuvant chemotherapy with the same drugs as for neoadjuvant chemotherapy. Histology of the resected specimen showed that almost all tumor cells were necrotized. Neither recurrence nor metastasis was found after 4 years. Our experience suggests that neoadjuvant chemotherapy, such as the one used here, would be exceedingly effective for SCO without serious non-hematological toxicities.

Small cell osteosarcoma (SCO), composed of small round cells, which mimic Ewing sarcoma cells (1), is the most rare variant of osteosarcoma, comprising approximately 1.3% of all osteosarcomas (1, 2). Nakajima et al. (1) have reported that chemotherapy in addition to surgery improves the prognosis of patients with SCO although the number of cases analyzed in their study was small due to the rarity of this disease. Regarding chemotherapy for osteosarcoma, four drugs, such as methotrexate, doxorubicin, cisplatin and ifosfamide have generally been used and the best disease-free-survival rate has been achieved by a combination of all four drugs (3, 4). However, toxicities occur in a substantial population of osteosarcoma patients (3, 5, 6, 7). In particular, cisplatin causes irreversible renal impairment and ototoxicity (5) and doxorubicin causes cardiac failure.

Recently, it has been reported that carboplatin (8) and pirarubicin (9) can be used for the treatment of osteosarcomas instead of cisplatin and doxorubicin, respectively, with less toxicity. Therefore, we modified the regimen of chemotherapy of the Italian and Scandinavian sarcoma groups (3), which comprises high-dose ifosfamide, high-dose methotrexate, cisplatin and doxorubicin and we adopted a new regimen of chemotherapy for osteosarcoma comprising of high-dose ifosfamide, high-dose methotrexate, in combination with pirarubicin and carboplatin to reduce toxicities.

Here, we present a case of localized tibial SCO, which was successfully treated with preoperative (neoadjuvant) chemotherapy using this new regimen, followed by tibial lengthening. Furthermore, we discuss the clinical manifestations and treatment.

Case Report

An 11-year-old boy noted a tender mass in the proximal left lower leg. The pain developed gradually over 2 months. The patient was diagnosed with a tibial tumor by radiographs at the regional hospital before being referred to the Bone and Soft Tumor Section of the Department of Orthopedic Surgery, Hyogo College of Medicine. On physical examination, a painful tumefaction was found, with slight local heat in the proximal tibia. Radiographs showed a mixture of osteolytic and osteosclerotic lesions in the metaphyseal region of the proximal tibia, suggesting osteosarcoma (Figure 1). Computed
Tomographic (CT) images clearly demonstrated osteolytic and osteosclerotic lesions, with partial cortical destruction and fracture (Figure 2). Magnetic resonance imaging (MRI) revealed an abnormal signal intensity in the metaphyseal region and an extraneous mass. The tumor had invaded beyond the growth plate into the epiphysis. The size of the tumor was 11×6×4 cm (Figure 3). Clinically, no metastasis was found. An open biopsy of the tibial lesion was performed. Histological examination revealed that the lesion was composed of predominantly small round cells producing mucous matrix (Figure 4). The EWS-FLI1 chimeric fusion gene transcripts, which clinically characterize Ewing sarcoma, were not detected by reverse transcription-polymerase chain reaction analysis. Finally, based upon radiological, histological, and genetic findings, an SCO of the proximal tibia was diagnosed.

Neoadjuvant chemotherapy, comprising high-dose ifosfamide, high-dose methotrexate, pirarubicin and carboplatin, was administered. The drugs were given sequentially as follows: methotrexate at 12000 mg/m²/day and pirarubicin at 30 mg/m²/day for 2 days, carboplatin at 150 mg/m²/day for 2 days, and ifosfamide at 3000 mg/m²/day for 5 days.

After three cycles of the chemotherapy, the painful tumefaction disappeared. MRI showed that the extraneous mass had completely vanished (Figure 5). In addition, the tumor uptake in bone scintigraphy disappeared. According to physical and radiological examinations, the neoadjuvant chemotherapy was effective. Regarding complications of chemotherapy, leucopenia (grade 4) causing a neutropenic fever occurred as a hematologic toxicity after two cycles of the neoadjuvant chemotherapy, and treatment with granulocyte colony-stimulating factor was required. However, non-hematological toxicities, including ototoxicity, renal impairment and cardiac failure, did not occur. An en-bloc, wide resection was performed, followed by tibial lengthening using the Ilizarov method. Intraepiphysyeal excision was carried out to obtain margins free of tumor invasion into the epiphysis (10). The patellar tendon was reattached to the soft tissue of the tibia. Macroscopically, the resected tissue consisted of white fibrous tissue, suggesting the effectiveness of the neoadjuvant chemotherapy. Histological examination clearly revealed the osteoid formation, which provides histological evidence of SCO. An almost complete response (a necrotic area of more than 90%) was achieved by the neoadjuvant chemotherapy (Figure 6). In addition, two courses of postoperative (adjuvant) chemotherapy, comprising of the same drugs as for the neoadjuvant chemotherapy, were started 10 days after surgery.
The length of the defect produced by the excision of the tumor was 13 cm. Distraction osteogenesis by modified bone transport was applied to regenerate the new bone into the defect by the use of an Ilizarov external fixator (Smith and Nephew, Memphis, TN, USA) (10). Distraction was started 7 days after the initial surgery at 0.5 mm, twice daily. The external fixation index (EFI), which was obtained by dividing the external fixation time by the length of distraction, was 32 days/cm. The external fixator was removed when sufficient bone regeneration had been obtained (Figure 7). On the same day, iliac bone grafting between the middle and proximal segments of the tibia (docking site) was performed followed by internal fixation with two plates and screws.

At the last follow-up, the patient needed a 2-cm shoe lift for leg length discrepancy of 3 cm (Figure 8). The active range of motion of the knee was from 0 to 110 degrees. The limb function was evaluated by the scoring system of the Musculoskeletal Tumor Society (MSTS) (11). The score is based on six categories: pain, function, emotional acceptance, activity, self-image, and complications.

Figure 3. A coronal T1-weighted MRI (left) shows an expansive mass with low to intermediate signal intensity area in the metaphyseal region and the extraosseous mass (arrows). The tumor has invaded beyond the growth plate into the epiphysis (arrowhead). An axial T2-weighted MRI (right) demonstrates the intraosseous and extraosseous extent of the tumor.

Figure 4. Histology shows the tumor consisting of neoplastic small round cells (Bar=100 μm).
supports, walking abilities and gait; the scores for each category (1-5) are added and presented as a percentage of maximum scores obtainable. A higher percentage means better function. The functional score was 73%, indicating that functional recovery was successfully achieved. Neither recurrence nor metastases have been found 4 years after the surgery.

Discussion

The prognosis of patients with non-metastatic conventional osteosarcoma of the extremity has been improved dramatically with the introduction of multidrug neoadjuvant chemotherapy in combination with surgical removal of the tumor (3, 12). The present article is the first report to show a case of non-metastatic tibial SCO successfully treated by neoadjuvant chemotherapy with high-dose ifosfamide, high-dose methotrexate in combination with pirarubicin and carboplatin.

SCO was first reported by Sim in 1979 (13). More than 50% of the patients are in the second and third decades of life (1). The most common location is the metaphysis of the long bones, and the distal femur is affected in 33% (24 out of 73 patients), followed by the proximal tibia in 12% (9 out of 73 patients) (14). Based upon patient series (1, 14), SCOs affect patients of the same age group and anatomical location as conventional osteosarcomas.

The clinical and radiological findings of SCO resemble those of the conventional osteosarcoma. Clinically, the common symptoms are pain and swelling (1, 14). Radiographically, there is a mixture of osteolytic and osteosclerotic lesions, which is not different from those of conventional osteosarcomas. Mineralized lesions are observed in most SCOs, either intramedullary and/or in extraosseous lesions, strongly suggesting a diagnosis of osteosarcoma rather than Ewing sarcoma. In the present case, intramedullary osteosclerosis was detected by radiographic and CT images.

In the histological diagnosis of SCO, the osteoid formation is an essential finding since this is not seen in
Ewing sarcoma (1, 13, 14). The histological diagnosis of SCO can be difficult since SCO sometimes produces only scant osteoid lesions. In such cases, the EWS-FLI1 chimeric fusion gene transcripts, which clinically characterize Ewing sarcoma, could facilitate differentiation of SCO from Ewing sarcoma, in conjunction with radiological findings.

Regarding the neoadjuvant chemotherapy of patients with non-metastatic osteosarcomas of the extremity, the Italian and Scandinavian sarcoma groups first presented a regimen for neoadjuvant chemotherapy consisting of two cycles of high-dose methotrexate (12 g/m²), cisplatin (120 mg/m²), doxorubicin (75 mg/m²) and high-dose ifosfamide (15 g/m²). Postoperatively, patients received two cycles of doxorubicin (90 mg/m²), and three cycles of high-dose ifosfamide, methotrexate and cisplatin. The results were promising: the 5-year probability of event-free survival was 64% (95% confidential intervals=57% to 71%) and overall survival was 77% (95% confidential intervals=67% to 81%). However, the incidence of non-hematologic toxicities was high, with ototoxicity, renal impairment and cardiac failure being 40%, 10% and 0.4%, respectively (3). Since carboplatin (8) and pirarubicin (9) can be used for treatment of osteosarcomas instead of cisplatin and doxorubicin, respectively, with less toxicity, we modified the regimen of neoadjuvant chemotherapy of the Italian and Scandinavian sarcoma groups and adopted a new regimen of chemotherapy for osteosarcoma comprising high-dose ifosfamide, high-dose methotrexate, in combination with pirarubicin and araplatin to reduce toxicities. As expected, in the present case, the neoadjuvant chemotherapy of our regimen resulted in the necrosis of almost all tumor cells, without causing non-hematological toxicities and thus enabling safe limb salvage.

In the treatment of limb salvage in a skeletally immature child, functional impairment due to subsequent limb-length

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Figure 7. The defect after excision of the tumor can be seen (left). Sequential radiographs at 2 weeks and 2, 4, and 11 months after the surgery show reconstruction with bone transport brought out by the Ilizarov technique (right).
discrepancy must be considered. Recently, we reported that satisfactory function could be maintained despite a frequent requirement for limb-lengthening surgery in the femur (15). In the present case, the patient regained satisfactory functional outcome after tibia lengthening. However, he will need additional limb lengthening until or just after skeletal maturity.

In conclusion, even though SCO is a rare subtype of osteosarcoma, it should be kept in mind as one of the differential diagnoses from Ewing sarcoma. In the treatment of SCO, high-dose methotrexate, high-dose ifosfamide in addition to carboplatin and pirarubicin as neoadjuvant chemotherapy should be considered, in order to obtain good local control with less toxicity and to improve prognosis.

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References


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