Dramatic Response to Cisplatin Window Therapy in a Boy With Advanced Metastatic Ewing Sarcoma

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Summary: Ewing sarcoma (ES) is the second most common type of primary bone malignancy, and retains a high propensity to metastasize; the prognosis of patients with disseminated disease is very poor, with an event-free survival rate of <20%. Current multimodality treatment for ES consists of combined chemotherapy before and concurrent with surgery and local radiotherapy for the involved bone. Cisplatin is one of the most widely used drugs for the treatment of bone tumors in children, but is not currently used in ES. We describe a child with multifocal ES, treated with a phase II trial including a single-drug window therapy, which displayed a dramatic response to 2 courses of cisplatin and had a favorable outcome.

Key Words: Ewing sarcoma, advanced metastatic disease, window therapy, cisplatin, outcome

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Ewing sarcoma (ES) is the second most common bone malignancy in children and young adults, with a slight male predominance.[1] ES has a high propensity to metastasize, and about 25% of patients show disseminated involvement at the beginning of disease. Multimodal treatment approaches, including surgery, radiotherapy (RT), and intensive multidrug chemotherapy, have led to notable improvement in the outcome of patients with localized disease, up to about 70% of event-free survival (EFS).[2,3]

In contrast, the prognosis of patients with primary disseminated disease remains very poor, with an EFS of <20%.[4] Patients with primary pulmonary metastases show a better outcome than patients with primary bone and/or bone marrow involvement.[4–8] Conventional treatment regimens for localized ES generally consist of a combination of vincristine, actinomycin-D, cyclophosphamide, doxorubicin, ifosfamide, and etoposide. Adjunctive surgical resection with or without radiation therapy is used for local control. Most episodes of disease recurrence occur after completion of therapy, and most recurrences (approximately 80%) occur within 2 years from initial diagnosis.[9]

Cisplatin (CDDP) and other platinum compounds are widely used drugs for the treatment of solid tumors in adults and children, especially when failure of first-line therapy occurs, but data concerning its activity and efficacy are very limited in ES.

We describe an impressive response to front-line CDDP as a single drug in a child with metastatic ES with a favorable clinical outcome.

CASE REPORT

A 10-year-old African boy was admitted 10 months after the onset of left elbow pain, followed by progressive swelling. He was diagnosed with an osteosarcoma (small cell variant) of the left arm in a Nigerian Hospital. He did not receive any therapy in Nigeria because they concentrate the few economical resources available on patients with more chances of healing. An international committee organized a transfer abroad to verify the histologic diagnosis and to explore the possibility of a therapeutic approach.

On admission the boy showed a huge mass (circumference 43 cm, whereas the contralateral was 15 cm) in the left elbow, and packed lymph nodes, sized 6×8 cm, were palpable in the left armpit (Figs. 1A, B). Other enlarged lymph nodes were palpable just over the left collar-bone. A painful subcutaneous nodule, sized 3×2 cm, was palpable in the left shoulder blade region. The left knee compression was painful. The abdomen, heart, and chest were unremarkable; no hepatosplenomegaly or skin lesions were observed.

Laboratory findings showed lactic dehydrogenase levels to be 1951 U/L (normal value <480 U/L).

A computed tomography (CT) scan showed a large osteolytic lesion of the distal humerus and proximal radius and ulna surrounded by proliferating soft tissue. Total body CT scan and ^{99}Tc-MDP bone scan showed a large mass of metastatic packed lymph nodes in the left armpit and skeletal metastases to the proximal region of the left humerus, to the fourth left rib, on the inferior region of the left shoulder blade and on the left knee. Bone marrow biopsy and aspirate were normal.

An open biopsy of the elbow mass was done. Histologically, the tumor was characterized by a monomorphic proliferation of small round cells with regular nuclei, finely dispersed chromatin, and inconspicuous nucleoli (Figs. 2A, B). Cytoplasm was scant and slightly eosinophilic with no matrix production. The tumor grew in a diffuse and sheet-like pattern infiltrating the cortical bone and lamellar bone of periosteal reaction and assumed lobular and filigree pattern in soft tissue invasion with necrosis (Fig. 2C).

The cells showed strong and diffuse membranous immunoreactivity toward cell-surface glycoprotein CD99 (Fig. 2D).

Reverse transcriptase polymerase chain reaction analysis of ES was performed from paraffin-embedded tissue. Molecular studies showed the characteristic translocation leading to a fusion of the ES gene (EWS) on 22q12 as to a member of the ES family transcription factors, which in our case was FLI1.

In conclusion, a diagnosis of ES with multiple skeletal and lymph node metastases was reached. The patient was enrolled in a joint trial of ISG and AIEOP for patients with multicenter ES at onset, called ISG-AIEOP/VHR-EW 02 protocol, consisting of a

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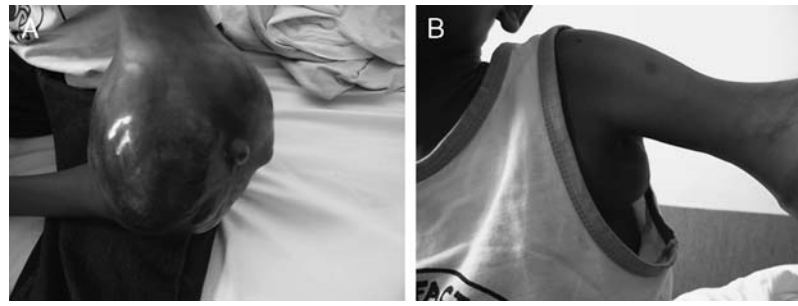

FIGURE 1. A, On admission the boy presented an impressive huge mass of the left elbow, having a circumference of about 43 cm. B, Packed lymph nodes, sized 6 × 8 cm, were palpable in the left armpit.

front-line with 2 courses of CDDP 100 mg/m^2 by 48-hour continuous infusion 3 weeks apart, followed by 8 courses of combined chemotherapy, a consolidation phase with myeloablative busulfan + melphalan, and local treatment on the site of the primary tumor, according to the same strategy adopted in the previous ISG/AIEOP VHR-EW 01 protocol, in which the front-line consisted of melphalan.[10]

The front-line CDDP courses were well tolerated without any severe side effect. After the second course of therapy with CDDP, the elbow circumference decreased to 28 cm (Fig. 3A); supraclavicular lymph nodes disappeared and axillary reduced to < 1 cm. Levels of lactic dehydrogenase fell below 500 IU/L.

The reevaluation by CT scan of the chest and left arm, total body scan with ^{99}Tc-MDP, and magnetic resonance imaging of the left arm, showed a very good response to treatment, with a very impressive reduction of the primary tumor size and a complete disappearance of the metastatic lymphadenopathy. A residual abnormal uptake in the ^{99}Tc-MDP bone scan on the left knee and left humerus was documented.

The patient underwent a subsequent phase with 8 intensive courses of chemotherapy. Collection of hematopoietic stem cells was done by leukapheresis after first course of cyclophosphamide 4 g/m^2 + etoposide 600 mg/m^2 (overall the fourth course), followed by filgrastim at a dose of 10 μg/m^2/d, according to the protocol. A total of 4×10^8 nucleated cells and 8×10^6 CD34$^+$ cells were collected.

Evaluation after the last course of chemotherapy, preceding the myeloablative treatment, showed an elbow circumference of 17 cm (Fig. 3B), whereas CT scan and magnetic resonance imaging of the elbow confirmed marked reduction of the tumor. Total body bone scan with ^{99}Tc-MDP showed a residual uptake on the left elbow without other metastatic locations.

To obtain the best control of the disease, we proposed demolitive surgery consisting of amputation of the left arm. The mother of the patient refused surgery, and for this reason we decided to give exclusive RT for local control, which was delayed until after the myeloablative phase. The patient received the consolidation phase with busulfan (1 mg/kg × 16 doses) and melphalan (140 mg/m^2), followed by autologous peripheral blood stem cell transplantation, with a normal take of polymorphonucleates and thrombocytes and without acute complications.

RT on the site of the primary tumor concluded the treatment program and consisted of 2 fractions of 1.2 Gy/d, up to a total dose of 55.2 Gy. Now, 42 months after the beginning of treatment and 30 months after the end of therapy, the child is well and in continuous complete remission.

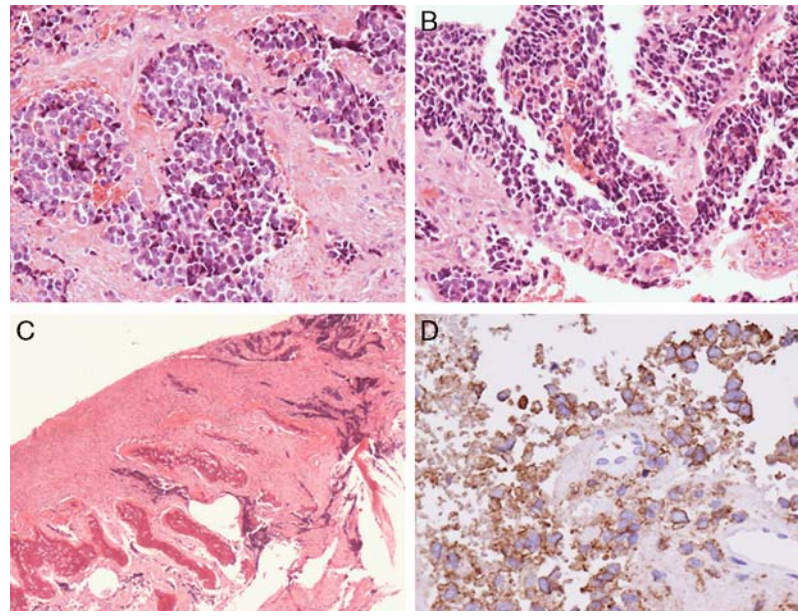

FIGURE 2. A and B, The tissue was characterized by a monomorphic proliferation of small round cells with regular nuclei, finely dispersed chromatin, and inconspicuous nucleoli. The cytoplasm was scant and slightly eosinophilic with no matrix production. C, The tumor grew in a diffuse and sheet-like pattern infiltrating the cortical bone and lamellar bone of periosteal reaction and assumed a lobular and filagree pattern in soft tissue invasion with necrosis. D, The cells showed strong and diffuse membranous immunoreactivity toward cell-surface glycoprotein CD99.

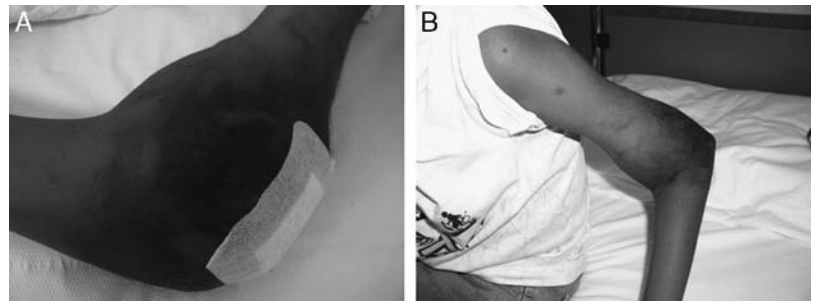

FIGURE 3. A, The boy showed a dramatic response to 2 courses of cisplatin therapy; elbow circumference reduced to 28 cm and the armpit lymphadenopathy regressed completely. B, Evaluation after the last course of chemotherapy, before the myeloablative treatment, showed an elbow circumference of 17 cm.

DISCUSSION

ES is the second most common bone malignancy in children and young adults, and prognosis of patients with disseminated disease other than pulmonary remains very poor, with an EFS of $<25\%$.

The introduction of combined modality treatment has determined a relevant improvement in the prognosis for many patients with ES. However, the results identified a bad prognosis of patients with large-volume primary tumors and metastatic disease. Our patient had both of these unfavorable prognostic characteristics, because he was admitted to our unit >10 months after the first signs and symptoms. The child, who was referred with a doubtful diagnosis of small cell osteosarcoma, was globally reevaluated, and histologic and molecular diagnosis of ES was correctly reached. The child was enrolled in the ISG-AIEOP/VHR-EW 02 protocol, consisting of a double course of high dose of CDDP window therapy, followed by intensive chemotherapy, myeloablative regimen, and autologous stem cell rescue. Response to CDDP alone, which is not generally used in clinical trials in first-line therapy, was very impressive, with a marked reduction of primary tumor size and metastatic disease.

In the literature, few phase II studies with CDDP in refractory solid tumors in children are reported, including ES. Overall, in these studies, of 27 patients with ES, only 2 objective responses were observed.[11–14] Platinum compounds have been used as first-line therapy in patients with ES, in a very limited number of studies, mostly in combination with other drugs, generally administered at doses of 70 to 100 mg/m^2, and some authors reported its effectiveness in the preoperative treatment of ES.[15–17]

In this patient the local treatment on the site of the primary consisted of RT alone. We are aware that a factor influencing the outcome in ES is surgery, which gives better results than RT alone in a nonlocalized ES setting, but surgery was not possible because his mother refused a demolitive surgical approach—arm amputation—because of religious reasons.[8]

In conclusion, the peculiarity of our case was the great sensitivity of the ES to CDDP. The patient had a favorable outcome and is now a long-term survivor. It is not possible to assess the contribution of the front-line CDDP to this favorable outcome, as this phase was part of an intensive and prolonged treatment approach, but our experience suggests that an aggressive treatment option may be justified even if the possibilities of cure seem extremely slim.

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