High-dose continuous infusion ifosfamide in the treatment of bone marrow infiltration with severe thrombocytopenia in a patient with Ewing sarcoma: a case report

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Abstract

Ewing sarcoma is a rare primary mesenchymal tumor of the bone that requires an intensive multimodal therapeutic approach. Multidrug chemotherapy regimens are also the backbone for relapsing/recurring Ewing sarcoma treatment, yet when relapse occurs as bone marrow infiltration, combination chemotherapy might be difficult to be administered and prognosis is poor. This report describes the case of a 22-year-old patient with Ewing sarcoma who developed severe pancytopenia due to bone marrow infiltration, who was treated with high-dose continuous infusion ifosfamide, obtaining both clinical, radiological and hematological response lasting for about 7 months.

INTRODUCTION

Ewing sarcoma is the third most common bone sarcoma and the second most common malignant bone tumor in children and young adults, with an incidence of 0.1/100 000/year and a median age at diagnosis of 15 years. Most cases arise in the extremities, but axial skeleton and soft tissue origin are possible. [1] Histological diagnosis is supported by the detection of specific gene translocations, generally resulting in EWSR1-FLI1 fusion (EWS-RNA binding protein 1 - Friend leukemia integration 1 transcription factor) or, more rarely, in other ETS genes (Erythroblast Transformation-Specific) such as EWSR1-ERG fusion (ETS Related Gene). [2] With the introduction of multiagent perioperative chemotherapy, including vincristine, doxorubicin, cyclophosphamide, ifosfamide and etoposide, 5-year OS increased to 65-70% in localized disease. [1] About 25% of patients present at diagnosis with advanced disease at diagnosis: most frequently involved sites are lung, bone and bone marrow. For this reason, an accurate skeletal staging with positron emission tomography (PET-CT) is mandatory and, in doubt cases, it must be completed with bone marrow biopsy and aspirate. [3] Five-year overall survival in patients with metastatic disease ranges from 20 to 40% according to metastases site, with bone localizations conferring a poorer prognosis. [4]

Moreover, Ewing sarcoma recurrence with bone marrow involvement has been associated with very poor survival and unavoidable fatal outcome, in contrast to patients with multiple bone metastases but no marrow involvement [5]. High-dose ifosfamide has been recently demonstrated to be highly effective on recurrent disease, with other active regimens being cyclophosphamide and topotecan, temozolomide and irinotecan, and gemcitabine and docetaxel. [6] Here we present the case of a young male patient affected by extremity Ewing sarcoma recurring with bone marrow infiltration causing severe pancytopenia 15 months after the end of adjuvant chemotherapy.

CASE REPORT

In April 2019, a 22 year old male with no past medical history presented with increasing pain in the right pelvis and inferior limb. Pain was at first managed by his general practitioner with nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids with no clear clinical benefit. In February 2020, a magnetic resonance (MRI) of right hip bone was performed, which detected a 9cm lesion extended from the femoral head to the bone neck, hyperintense on T2-weighted images suggesting intraspongious edema. A computed-tomography (CT) scan subsequently performed confirmed the presence of a vast, irregular osteolytic area and a hyperdense tissue in the great trochanter region, with a maximum depth of 15mm. In March 2020, a biopsy of the osteolytic area was performed: the histological specimen showed a proliferation of undifferentiated, small round cell positive for CD99, FLI1, vimentin and focal CD56, suggestive of Ewing sarcoma. The molecular analysis confirmed the presence of EWSR1-ERG rearrangement (21q22.2). Staging chest and abdomen CT and PET-CT scan did not detect any distant metastases; right femur head, neck, intertrochanteric region and proximal diaphysis showed a pathological hypermetabolism (SUV max 7.16), but bone marrow fine needle aspiration was negative for neoplastic cells. From April to June 2020, patient received four courses of induction chemotherapy: two cycles of vincristine, doxorubicin and cyclophosphamide (VDC), one cycle of vincristine, actinomycin-D and ifosfamide (VAI) and one cycle of etoposide and ifosfamide (IE). The following radiological assessment (chest, abdomen and right inferior limb CT scan and right hip MRI) showed disease stability. In July 2020, patient underwent surgical resection of right femur and global modular replacement system prosthesis implant. Pathological response was good, although not complete, with a 95% necrosis rate and 5% of residual sarcomatous cells. Between August 2020 and March 2021, the patient received adjuvant chemotherapy: 3 cycles of VDC, 3 cycles of VAI and 3 cycles of IE. Afterwards, follow up was started with trimestral chest, abdomen and right inferior limb CT scan and blood tests. Radiological assessments didn't detect any signs of disease relapse; blood samples showed persistently stable G2 neutropenia, G1 anemia and G1 lymphocytopenia, consistent with recent chemotherapy. The patient experienced slowly increasing pain at his right thigh, refractory to analgesics and opioids. After one year, in August 2022, blood tests showed pancytopenia, with neutropenia G1 (N 1750 /mm3), lymphocytopenia G1 (LYMPH 0.97/mm3), thrombocytopenia G2 (PLT 74000/mm3) and anemia G1 (11.4 g/dl). Lactate dehydrogenase (655 U/L) and ferritin (1505 ug/l) levels were increased. Peripheral blood smear identified the presence of immature cells (myelocytes 4%, metamyelocytes 0.5%). Lymphocytes flow cytometry analysis, vitamin B12, protein electrophoresis, alkaline phosphatase, renal and hepatic function were preserved. At this time, MRI of right inferior limb displayed intraspongious edema of iliopubic branch, CT scan was persistently negative. No signs of recent bleeding were objectifiable. A bone marrow fine needle aspiration and a biopsy were then performed. The myelogram showed the presence of big, pleomorphic non hematopoietic cells. Ewing sarcoma bone marrow relapse was confirmed by the biopsy, where most bone marrow space was occupied by a high-grade neoplasm composed of small round cells, arranged in sheets, characterized by monotonous nuclear appearance and scant cytoplasm with focal areas of cytoplasmic clearing. Brisk mitotic activity, areas of hemorrhage and necrosis were present throughout the biopsy specimen. By immunohistochemistry, the neoplastic cells showed strong crisp membranous CD99 immunostaining and diffuse NKX2.2 nuclear immunopositivity. Conversely, terminal deoxynucleotidyl transferase (TdT), desmin and myogenin (Myf4) were negative. [Figure 1] A PET-CT was then performed, showing an intense bone marrow glucidic hypermetabolism in spine, scapulae, sternum, ribs, hipbone, humeri and femurs. At the end of August 2022 blood cell counts rapidly dropped (in particular, Hb 8 g/dL, PLT 33.000/mm3). Given the low blood cell counts which contraindicated standard polychemotherapy regimens, we decided to start first line chemotherapy with high dose ifosfamide at the dose of 1g/m2 per day, administered as a continuous infusion over 14 days, followed by a 14 days pause. The first course of such chemotherapy was started on August 24, 2022, with a 50% precautionary dose-reduction (total dose: 7 g/m2 over 2 weeks). A strict, daily monitoring of blood count was performed both during infusion and in the 2 weeks off; toxicity nadir was reached on day 17, with anemia G3 (7.3 g/dl) and thrombocytopenia G4 (PLT 21000 /mm3). Persistent hematological toxicity required one platelet and multiple red blood cells transfusions. At the beginning of the second course, blood counts improved with neutrophil count back to normal, improved hemoglobin (10.3 g/dl) and lymphocyte count (0.82 /mm3) but persisting severe thrombocytopenia (32000 /mm3). Following the second course,

administered at the same reduced dose, platelet count started to slowly increase; no platelet and less red blood cell transfusions were needed. On the third cycle, thrombocytopenia was restored to G1 level (85000 /mm3), and chemotherapy dosage was increased to 80% (total dose 11 g/m2), with a good hematological and subjective tolerance. [Figure 2] After three cycles, PET-CT scan showed metabolic response. [Figure 3] Due to the persistently improved blood tests, and the normalization of platelet count, chemotherapy was prosecuted at full dose for three more cycles. Metabolic and hematological responses were associated with clinical benefit on pain and deambulation. In February 2023, after six total courses of high-dose ifosfamide, PET-CT showed progressive bone marrow disease and once again blood tests abruptly dropped, with G3 neutropenia, G2 lymphocytopenia, G1 anemia and G1 thrombocytopenia. Moreover, the patient developed vision problems, hyposthenia and hypoesthesia of lower limbs, and a brain MRI demonstrated a diffuse meningeal invasion. In March 2023, a new line of chemotherapy with Irinotecan and Temozolomide was started. Although it was administered at a reduced dose, therapy was complicated by persistent neutropenia G3 needing frequent treatment delays and dose adjustments. In July 2023, the patient was hospitalized due to paraparesis, acute urinary retention and pain; a CT scan confirmed new bone progression. He received palliative radiotherapy on painful sites and was started on oral etoposide with only minor benefits. Palliative care team was then involved, and the patient died two months later at home.

DISCUSSION

Thrombocytopenia is a frequent event in oncological patients. According to Common terminology criteria for adverse events (CTCAE) v5.0, it is defined as a decrease in number of platelets in a blood specimen, and 4 severity categories are recognized: grade 1 for counts ranging between the upper normal level and 75 $\times$ 10ˆ9/L, grade 2 between 75 and 50 x 10ˆ9/L, grade 3 between 50 and 25 x 10ˆ9/L and grade 4 under 25 x 10ˆ9/L. [7]

Its incidence is estimated to range from 10% to 68%, according to different studies. [8] About 21% of patients with hematologic malignancies and up to 6% of patients with solid tumors present thrombocytopenia before chemotherapy. The most frequently associated histotypes are acute leukemia (37.3%) and multiple myeloma (24.4%); among solid tumors, melanoma (21.4%), ovarian (14.7%) and lung (14.3%) cancer. After three months of chemotherapy, the reported incidence rates increase to 28.2% and 12.8% for hematological and solid neoplasms, respectively. [9]

Chemotherapy has a well-known impact on platelet and other blood cell counts, through an acute damage and apoptosis of hematopoietic cells. [10] Acute thrombocytopenia generally occurs within 10 days from the infusion and is of short duration due to the bone marrow replication reserve. [11] A long term bone marrow injury may occur when chemotherapy inhibits the self-renewal potential of hematopoietic stem cells, causing their senescence. [12, 13] Moreover, chemotherapy drugs may interfere with the hematopoietic microenvironment, resulting in bone marrow loss and adipogenic differentiation of stem cells. [14]

Gemcitabine is associated with the highest risk of thrombocytopenia, followed by platinum-based regimens; on the opposite, anthracyclines and taxanes have lower rates. [9, 15, 16] High dose ifosfamide has a well-known hematological toxicity, with a grade 3-4 thrombocytopenia occurrence rate of almost 30% in some studies [17] A recent study has also showed that a low platelet count was significantly associated with ifosfamide and etoposide chemotherapy in Ewing sarcoma patients. [18]

While most cases are asymptomatic, a decrease in platelet count may lead to minor and major bleeding, especially when platelet counts drop to grade 2 and lower. A study by Elting and colleagues demonstrated how bleeding episodes complicated 9% of chemotherapy cycles in patients with a history of previous bleeding and who had baseline platelet count lower than 75000/mm3, bone marrow metastases or poor performance status. [19]

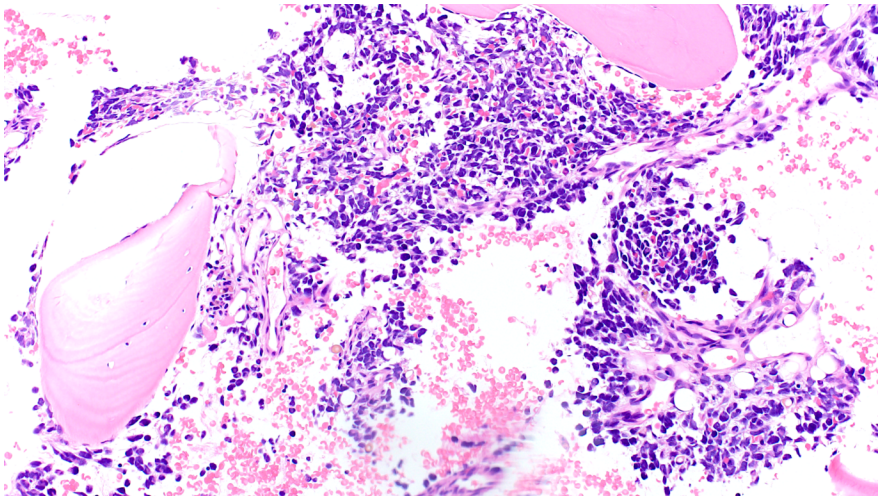
No clear guidelines on management of patients with bone marrow infiltration are available: most data are obtained by case reports or small retrospective studies of patients treated with different cytotoxics according to histology, with a great heterogeneity on outcomes. A French retrospective study showed the efficacy and feasibility of weekly, low dose paclitaxel in 26 patients with breast cancer BMI. [20] Similarly, analogous cases

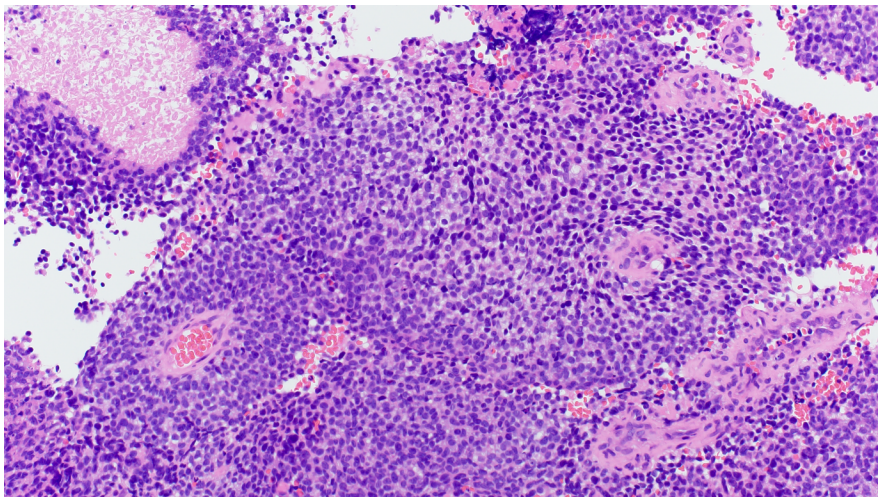
of breast cancer BMI have been successfully treated with continuous infusion doxorubicin [21] or weekly nab-paclitaxel [22]. On the other hand, a patient with neuroblastoma did not derive any benefit from combination therapy of standard dose topotecan and cyclophosphamide [23].

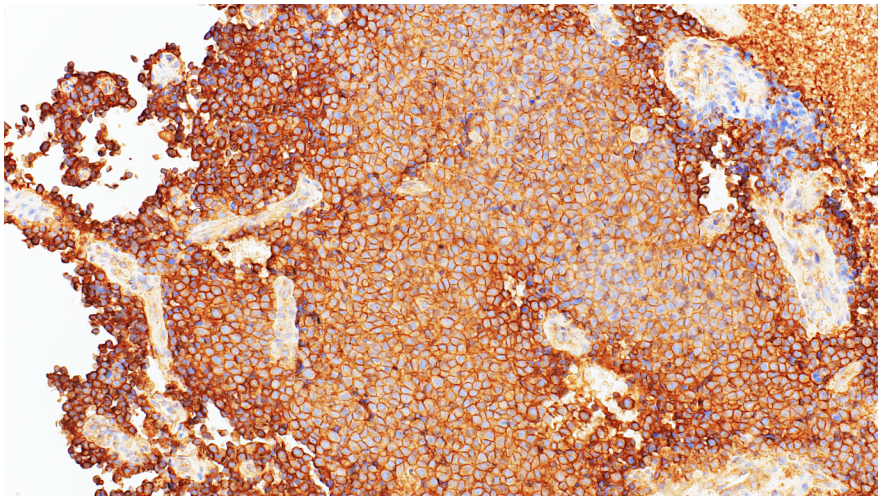
Among mesenchymal tumors, Ewing sarcoma and pediatric rhabdomyosarcoma BMI is not uncommon [24-25]; more rarely, bone marrow infiltration from other histologic subtypes like angiosarcoma [26], epithelioid sarcoma [27] and follicular dendritic cell sarcoma [28] has been reported. Given the aggressiveness of such sarcoma subtypes, most cases were treated with high dose, multidrug regimens with poor responses and severe hematological toxicity, often fatal. [29] Of note, one patient with alveolar rhabdomyosarcoma treated with schedule-adapted VDC/IE had an optimal response with 15-months PFS [30] Chemotherapy, acting on the very first cause of thrombocytopenia, surely has a leading role in the treatment of bone marrow infiltration. All the reported successful cases have in common the administration of low dose, continuous infusion or weekly fractionated chemotherapy regimens, with the aim of reducing the negative impact on hematopoietic bone marrow cells.

To our knowledge, this is the first described case of management of bone marrow infiltration from Ewing sarcoma presenting with severe thrombocytopenia successfully managed with low-dose continuous infusion ifosfamide, providing almost 7 months of progression-free survival.

Such results are highly clinically significant, considering the poor prognosis of relapsed Ewing sarcoma, and might be of help when decision-making is required in this setting.







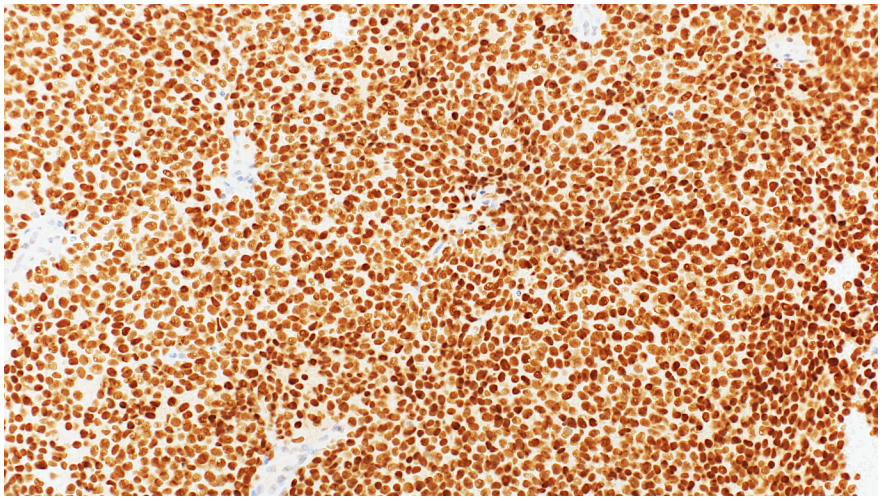


Figure 1. H&E bone marrow biopsy showing extensive infiltration by Ewing sarcoma. Small round cells with scant cytoplasm arranged in sheets fill the marrow space (1A and 1B). Strong membranous CD99 (1C) and diffused NKX2.2 (1D) immunopositivity.

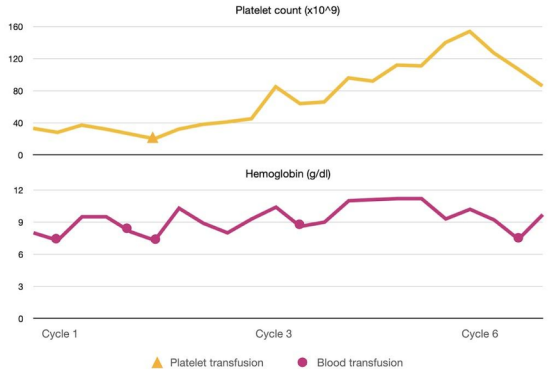
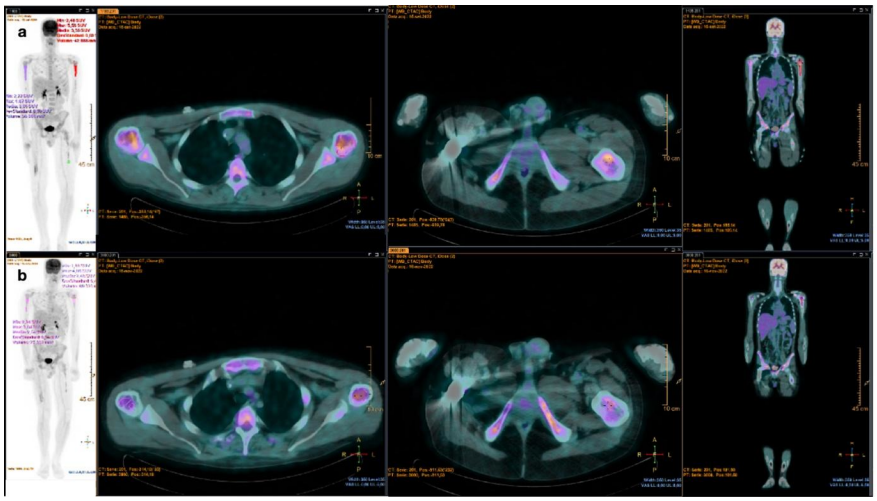


Figure 2. Platelet and hemoglobin levels during treatment with HD-ifosfamide and required transfusions. Blood tests progressively improved during treatment, until progression after cycle 6 when platelet count abruptly dropped.



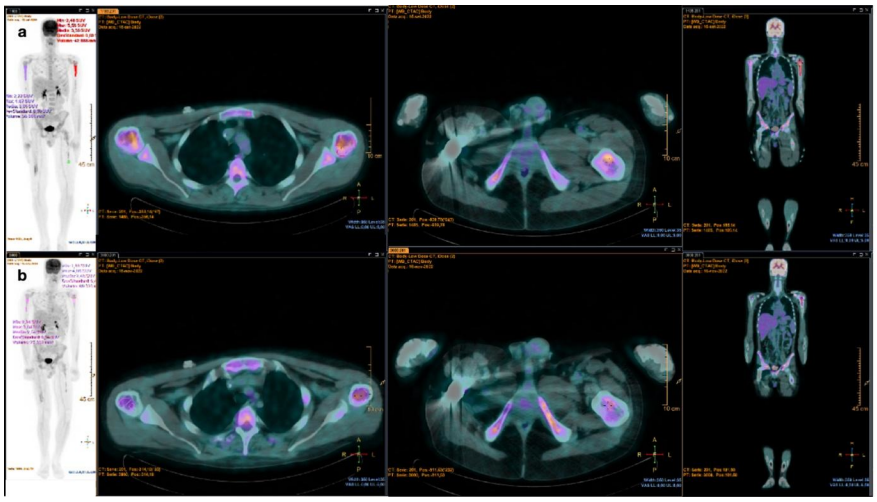


Figure 3. PET-CT performed before (a) and after (b) three cycles of HD-ifosfamide, showing metabolic response to treatment on bone marrow infiltration.

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