Osteosarcoma after bone marrow transplantation for acute lymphoblastic leukemia

Abstract A male patient initially diagnosed with acute lymphoblastic leukemia at age 9 years received chemotherapy (total body irradiation, 12Gy) followed by allogeneic bone marrow transplantation. Since then, he had been in complete remission. Three years after the bone marrow transplantation, he complained of increasing pain in the right knee. Radiological and histological examinations led to a diagnosis of conventional osteosarcoma. We performed intensive chemotherapy and wide local excision of the osteosarcoma. Intensive chemotherapy was accomplished as planned, although recovery from myelosuppression was delayed during some cycles. Polymerase chain reaction-single-strand conformation polymorphism analysis revealed a p53 gene mutation in exon 7 in the tumor cells, but not in skin or blood cells. This is an extremely rare case of osteosarcoma after bone marrow transplantation.

Key words Osteosarcoma · Acute lymphoblastic leukemia · Bone marrow transplantation · Secondary neoplasm · Total body irradiation · p53

Introduction

Bone marrow transplantation (BMT) is an increasingly effective treatment for leukemia and several other malignant and nonmalignant diseases.1-3 However, there is growing concern about compromised immune function and longterm adverse effects, particularly regarding new cancers, resulting from total-body irradiation (TBI) and high-dose chemotherapies used as conditioning regimens for transplantation.4-6

As a second malignancy after BMT, Curtis et al.7 observed only 1 case of osteosarcoma in 80 new cases of invasive solid tumors among 19229 patients who underwent BMT.

Here we report the case of a 13-year-old patient presenting with osteosarcoma 3 years after receiving chemotherapy, TBI, and BMT for T-cell acute lymphoblastic leukemia (T-ALL). Also, p53 gene mutations of exons 5–8 were analyzed, using polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP) followed by direct sequencing.

Case report

A male patient, at the age of 9 years, presented with spotty subcutaneous hemorrhage on his legs in May 1995. He was diagnosed with T-ALL, and cytogenetic analysis revealed a chromosomal change of 46XY,add(7)(q21.2). Chemotherapy was initiated according to the Osaka Childhood Leukemia Study Group (OCLSG) 94 protocol for the ultra high-risk group.8 This consisted of induction with dexamethasone, prednisolone, vincristine, pirarubicin, and l-asparaginase; consolidation with vindesine, cytarabine, pirarubicin, cyclophosphamide, and dexamethasone, followed by two courses of high-dose methotrexate; and maintenance (treatment 1) consisting of two pairs of drugs: mercaptopurine daily plus methotrexate weekly for 3 weeks, alternating with 1 week of prednisolone daily and vincristine once in the fourth week. After the confirmation of complete remission by bone marrow aspiration, the patient received TBI of 12Gy, with a 3-Gy additional dose for brain, and pretransplant conditioning with 3000mg/m² of cyclophosphamide and 600mg/m² of thiopeta. Subsequently, 5.5 months after diagnosis, he underwent allelo-
BMT from his HLA-identical brother. The cumulative doses of chemotherapeutic agents given prior to the BMT were as follows: vincristine, 7.5 mg/m²; pirarubicin, 120 mg/m²; l-asparaginase, 120 kU/m²; vindesine, 12 mg/m²; cyclophosphamide, 6200 mg/m²; etoposide, 1500 mg/m²; cytarabine, 1230 mg/m²; 6-mercaptopurine, 1575 mg/m²; methotrexate, 279 mg/m²; thiopeta, 600 mg/m²; dexamethasone, 736 mg/m²; and prednisolone, 600 mg/m². Since then the patient had been in complete remission. In September 1998, 3 years after the BMT, the patient complained of increasing pain in the right knee. Plain X-rays revealed a mixed sclerotic and lytic lesion with slight periosteal reaction in the metaphysis of the right tibia (Fig. 1). These findings were consistent with conventional osteosarcoma. On plain computerized tomography (CT), a large soft-tissue mass with patchy calcification was apparent (Fig. 2). Magnetic resonance imaging (MRI) revealed an isointense lesion, measuring 3.5 × 3.5 × 6.0 cm, accompanied by an intramedullary hypointense area, suggesting bone marrow edema, on T1-weighted images (Fig. 3a). The lesion was enhanced heterogeneously on post-contrast T1-weighted images, using gadolinium diethylenetriaminopentaacetic acid (Gd-DTPA) (Fig. 3c). T2-weighted images confirmed a heterogeneous hyperintense lesion (Fig. 3b).

Biopsy of the right proximal tibia led to a diagnosis of conventional osteoblastic osteosarcoma. The biopsy specimen was composed of spindle cells with anaplastic nuclei producing malignant osteoid matrix (Fig. 4). These findings were consistent with conventional osteosarcoma. On plain computerized tomography (CT), a large soft-tissue mass with patchy calcification was apparent (Fig. 2). Magnetic resonance imaging (MRI) revealed an isointense lesion, measuring 3.5 × 3.5 × 6.0 cm, accompanied by an intramedullary hypointense area, suggesting bone marrow edema, on T1-weighted images (Fig. 3a). The lesion was enhanced heterogeneously on post-contrast T1-weighted images, using gadolinium diethylenetriaminopentaacetic acid (Gd-DTPA) (Fig. 3c). T2-weighted images confirmed a heterogeneous hyperintense lesion (Fig. 3b).

Biopsy of the right proximal tibia led to a diagnosis of conventional osteoblastic osteosarcoma. The biopsy specimen was composed of spindle cells with anaplastic nuclei producing malignant osteoid matrix (Fig. 4). The patient was treated according to a modified OOS-C protocol. Preoperatively, this consisted of two courses of doxorubicin 90 mg/m² and cisplatinum 120 mg/m², and a course of high-dose ifosfamide, 15 g/m². Postoperative courses included two cycles of pirarubicin 90 mg/m² and cisplatinum 120 mg/m², with high-dose ifosfamide, 15 g/m², and two cycles of