A 25-year-old female with achondroplastic dwarfism, diagnosed when she was six months old, was diagnosed with chronic myeloid leukemia (CML) in chronic phase with 9;22 translocation, A2B3 gene rearrangement and a Sokal index of 0.5. A recombinant interferon-α2A treatment was started in October '94, which obtained a hematological, but not a karyotypic, response at the 6th and 12th month. In August '94, the patient was submitted to allogeneic bone marrow transplantation (alloBMT) from a 36-year-old matched sibling. The procedure was well tolerated. Disease-free survival (DFS) and overall survival (OS) were 21 and 39 months, respectively. We have not found any reported cases of achondroplastic patients submitted to alloBMT in the literature or in the IBMT Registry.

ABSTRACT

Achondroplasia is the most common type of genetic dwarfism, with a prevalence estimated between 0.1 and 1.5 per 10,000 births. It is characterized by a disproportionate short stature and other skeletal anomalies resulting from a defect in the maturation of the chondrocytes in the growth plate of cartilage. Recent studies have mapped the achondroplasia gene on chromosome region 4p16.3 and have identified a common mutation in the gene encoding the fibroblast growth factor receptor 3 (FGFR 3). The clinical and radiological features of this condition are at present well known, while the frequency and mutation rate had not been studied until ten years ago.

Chronic myeloid leukemia is a clonal hematopoietic disease resulting from the malignant transformation and expansion of a single pluripotent progenitor cell, characterized by the Philadelphia (Ph) chromosome or 9;22 translocation, which results in the formation of the bcr/abl fusion oncogene. Drugs such as busulfan and hydroxyurea, and more recently interferon-α, have been used to keep the hematologic manifestations of the disease under control, obtaining, with the latter, partial or complete cytogenetic remission and improvement of disease-free survival (DFS). Allogeneic bone marrow transplantation is the only treatment known to be curative, and is the procedure of choice for patients under the age of 50 with HLA-identical sibling donors. Here we reported the rare case of a young woman affected by congenital achondroplasia and chronic myeloid leukemia submitted to allogeneic bone marrow transplantation (alloBMT).

Case Report

The patient is a Caucasian female whose achondroplastic dwarfism was first diagnosed at the age of six months by X-rays of the skeleton. The mutation FGFR3 in our patient was not tested at diagnosis or subsequently. Clinical and radiographic characteristics included bowlegs and intoe varus, dolichocephalic, deep chiasmal sulcus, antiversion of the pelvis, lumbar hyperlordosis, dorsal and lumbar scoliosis, small head, biparietal bossing, flattened nose, microcystic hypertrichosis, curvature of the fibulae, frontal bossing, laxity of the ligaments. From the age of 12 to 17, she underwent eleven surgical interventions on the tibia, femora and rotula, with a height increase of about 16 cm (from 117 cm to 133 cm). Both for diagnosis and for control after the surgical interventions, the patient was subjected to several radiographies of the skeleton, for an approximate mean total dose to bone marrow of 10.62 mGy.

In June 1994, when the patient was 25 years old, she was diagnosed with CML in chronic phase with 9;22 translocation, A2B3 gene rearrangement and a Sokal index of 0.5. Physical examination at diagnosis was negative for lymphadenopathies and organomegalies.

From October '94 to July '95 the patient was treated with recombinant interferon-α2A, obtaining a hematological, but not a karyotypic, response at the 6th and 12th month. Considering the response to interferon-α2A and seeing that a consanguineous HLA, ABO, Rh identical sibling donor was available, the patient was submitted to alloBMT.

Disease-free survival (DFS) and overall survival (OS) were 21 and 39 months, respectively. We have not found any reported cases of achondroplastic patients submitted to alloBMT in the literature or in the IBMT Registry.

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cal sibling (36-year-old sister) was available, the patient was subjected to an alloBMT. The pulmonary, cardiac, hepatic, renal and renal functions evaluated before the transplant were normal. In August ‘95, the patient underwent BMT. The conditioning regimen included BUS 16 mg/kg/dy p.o. for 4 days and CTX 60 mg/kg/day intravenously for 2 days. GVHD prophylaxis consisted of CyA for 13 months with a short course of MTX (15 mg/m² on day +1, 10 mg/m² on day +3, +6, +11). Bone marrow was reinfused on August 7, 1995, with a total of 1.7×10⁹/kg nucleated cells, 0.4×10⁹/kg mononuclear cells and 17.6×10⁴ CD3-positive lymphocytes. On day +14, the patient developed a grade I, stage II cutaneous acute GVHD. The time to achieve granulocytes >0.5×10⁹/L and a stable platelet engraftment was 21 days. On day +29, she was discharged from the hospital.

The follow-up after BMT was complicated by severe hypogammaglobulinemia and recurrent respiratory infections. Four months after BMT the patient presented a chronic hepatic GVHD. In November 1996, 15 months after BMT, she developed an autoimmune thyroidite treated by substitutive therapy.

Cytogenetic and molecular analysis, tested at 3, 6, 9, 11, 13 and 21 months after BMT, were normal. DFS and overall survival (OS) were 21 and 39 months, respectively.

**Discussion**

Treatment with conventional chemotherapy usually fails to produce a persistent, complete remission in CML, and does not prevent progression to accelerated phases and blast crisis, which occur after a median of 4 years. More recently, interferon-α has been shown to improve disease-free survival and induce a partial or complete cytogenetic remission. Bone marrow transplantation (BMT) may prolong survival and, in some cases, provide curative therapy for CML patients under the age of 60 with HLA-identical sibling donors.

At a younger recipient age, transplants within one year of diagnosis in chronic rather than advanced phases provide a better outcome. Graft versus host disease (GVHD), pneumonia and systemic infections are commonly encountered complications.

Up to now, no case of achondroplasia and CML had been described, and a correlation between the two pathologies has not been proved. On the contrary, a correlation between radiation and tumor is well known, and CML is a clonal proliferative disorder of the hematopoietic stem cell that can develop after exposure to a high dose of radiation. Comprehensive reviews of the carcinogenic effects of radiation have been published. In children exposed to radiation, excess risks may take much longer to emerge than in adults with similar exposure. There is consistent evidence that the excess risk of leukemia per unit radiation dose is much higher at low doses than at high doses administered for the treatment of malignant disease. Almost all types of cancer can be caused by exposure to ionizing radiation; certain sites, such as the thyroid, the female breast and the bone marrow, appear to be more radiosensitive than others. Radiation-related leukemia risk depends on the number of parameters, such as radiation dose to the active bone marrow dose rate, and the percentage of marrow exposed. At the age of 6 months and subsequently at the age of six years, our patient was submitted to an approximate mean total dose to bone marrow of 10.62 mGy with a significant carcinogenic risk calculated retrospectively in a study by the Medical Physic Department of Udine.

A CML was diagnosed 18 years after the first radiography; it is possible to hypothesize a correlation between the total dose of radiation and its leukemogenic effects.

The patient was submitted to alloBMT because of the hematological response to interferon-α2A, and the fact that a consanguineous HLA identical sibling was available, and because long-term (5 years) disease-free survival (DFS) was observed in over 65% of the patients transplanted early in the course of the disease in chronic phase. No other cases of achondroplastic patients with CML subjected to alloBMT have been reported in the literature or in the IBMT Registry. Following the recommendations of the IBMT Registry, the conditioning regimen was modified, reducing the CTX dosage by half.

The BMT was well tolerated without significant increase in toxicity and complications.

**Reference**