ACUTE LYMPHOBLASTIC LEUKEMIA OCCURRING AS A SECOND MALIGNANT NEOPLASM IN A CHILD

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Abstract: The effective treatment of childhood malignancies has increased the importance of early detection and treatment of second malignant neoplasms. Anticancer drugs may also be leukemogenic agents, by the same mechanisms that kill cancer cells. We report the case of a 10-year-old boy who had received radiotherapy and chemotherapy for the treatment of Ewing's sarcoma and developed acute lymphoblastic leukemia 22 months after the diagnosis of primary malignancy. Although chemotherapy is well known to potentiate the development of second acute nonlymphocytic leukemia, the pathogenic factors leading to second acute lymphoblastic leukemia remain obscure.

Case Report

This 10-year-old boy had the initial presentations of scalp and neck masses in November 1996. After surgical excision of scalp lesions, histologic examination confirmed the diagnosis of Ewing's sarcoma. Computerized tomography of the head, neck, chest, abdomen, and pelvis revealed neck lymphadenopathy. The results of bone scan and bone marrow aspiration/biopsy were unremarkable. Under the diagnosis of extraosseous Ewing's sarcoma with metastases to neck lymph nodes, the boy was treated with 14 cycles of combination chemotherapy consisting of vincristine, actinomycin D, and cyclophosphamide from 1996 to 1998. The cumulative doses of drugs administered were 57 mg/m² vincristine, 0.9 mg/kg actinomycin D, and 30.8 g/m² cyclophosphamide. He also received two courses of radiotherapy (2,000 cGy for each course), one to the left cervical lymph node chain for metastases and the other to the left scalp for local recurrence of the original tumor. After completion of the chemoradiotherapy, there was no evidence of residual tumor. The boy remained well until 3 months after cessation of chemotherapy and 22 months after the first diagnosis of primary malignancy, when he was sent to our hospital due to nasal bleeding. Pancytopenia (white blood cell count, 2.98 x 10⁹/L; hemoglobin; 1.29 mmol/L; platelets, 79 x 10⁹/L) and 50% blastic cells in peripheral blood were noted. Bone marrow aspirate disclosed 90% blasts that were myeloperoxidase-negative and of L2 morphology by the French-American-British classification. Immunologic study by fluorescence-activated cell sorting analysis demonstrated that the blasts expressed CD10 (100%), CD19 (100%), and CD34 (85%) antigens in addition to HLA-DR (100%), but lacked CD20 (8%), CD7 (1%), CD2 (0%), CD13 (2%), CD33 (0%), and CD15 (0%) antigens. Cytogenetic analysis showed a karyotype 50-51,
X, +X, −Y, t(2;7)(p13;q22), +4, +del(6)(q13q27), del(12)(q15q24), +14, (17)(q10), +21, +21. Induction chemotherapy was instituted with vincristine, epirubicin, L-asparaginase, VP-16, cytosine arabinoside, and prednisolone. Although remission was attained after induction chemotherapy, relapse occurred about 5 months later and the boy died of sepsis in August 1999.

Discussion

The cumulative probability of developing a second leukemia has been estimated to reach 0.8%–20 years after initial diagnosis of childhood cancer, with a mean latency of 3.5 years [5]. Generally, the latent period of second leukemia is shorter than that of second solid tumor [2, 3]. Chemotherapy is more contributive to second leukemia than radiotherapy [5, 8]. Second leukemia is characterized by a preleukemic phase, a high association with cytogenetic abnormalities, a poor response to chemotherapy, and generally an ominous prognosis [4].

Most cases of second leukemia occur as AML or MDS [4, 5]; only sporadic cases were described as second ALL [6, 7]. Although a myelodysplastic phase often precedes the second AML/MDS, no such preleukemic phase is detected in second ALL. The outcome of patients with second ALL is usually poor, even in cases with a good initial response to chemotherapy [7]. As conventional therapy for second ALL is usually unsuccessful, a more intensive modality may be needed.

Second leukemia may be caused by chemotherapy and/or radiotherapy, genetic susceptibility, or just chance. It has been demonstrated that alkylating agents can induce second AML/MDS in patients with partial or complete deletions of chromosomes 5 and/or 7 [4, 9]. The epipodophyllotoxins that act as DNA topoisomerase II inhibitors most often cause chromosomal translocations involving band 11q23 with breakpoints within the MLL gene [10, 11]. Anthracycline agents and actinomycin D also disturb the interaction between DNA and topoisomerase II in the MLL gene [12].

The hyperdiploidy with gain of chromosome 4 and 21 in this case may have been the determinant of the development of second ALL, since the relationship between ALL and chromosomes 4 and 21 is well established [13, 14]. The association of t(2;7)(p13q22) with second ALL, which was found in the leukemic cells from our patient, remains to be explored.

Genetic predisposition to cancer was described by Li and Fraumeni in 1969 [15]. Mutation of the tumor suppressor gene p53 seems to be the common pathogenetic mechanism [16]. Second ALL has been observed in neurofibromatosis type I patients and after primary malignancy of Wilms’ tumor or retinoblastoma, which all have a constitutional susceptibility to cancer development [6]. Nevertheless, our patient did not have a family history of cancer described in the patients of Li and Fraumeni. In addition, Ewing’s sarcoma and second ALL are rarely associated with p53 mutation [17, 18].

It has been argued that second leukemia may be part of the natural course of the primary cancer, like the coincidence of osteosarcoma and retinoblastoma that results from the same genetic abnormality. Ewing’s sarcoma has the characteristic translocation t(11;22) (q24;q12) [19]. Chromosomal translocation (11;22) (q24;q12) has never been reported in denovo or second leukemia [20].

The primary malignancies that can precede second ALL are diverse [6]. Primary malignancy seems to have less impact on the development of second ALL, and second ALL following various primary malignancies is similarly rare, although a limited number of cases have been reported. In addition, children with second ALL had no obvious association with any particular treatment modality or chemotherapy agent [6]. Estimation of the risk factors for developing second ALL can only be adequately accomplished with a large cohort in a case control study. However, the rarity of second ALL after the same therapy for a primary malignancy may imply that host genetic susceptibility combined with the leukemogenic effect of chemotherapy plays a critical role in the development of second ALL.

References