Toxicity and Outcome of Intensive Chemotherapy for Acute Lymphoblastic Leukemia Complicated with Turner's Syndrome

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Abstract

A 17-year-old woman was diagnosed as acute lymphoblastic leukemia (ALL). As she had chromosomal abnormalities of 44, XO, der(9)t(3;9)(q11;p13), der(10;19)(q10;p10), del(15)(q15), -16, -19, +22 with the presence of ovarian dysplasia and abnormal physical features, a diagnosis of Turner's syndrome was made. She received an induction chemotherapy, which consisted of daunorubicin, cyclophosphamide, vincristine, L-asparaginase and prednisolone. Although, severe liver dysfunction was observed, the patient achieved a complete remission (CR) on day 31 following chemotherapy and has maintained CR for more than five years. The recording of such cases may well be of value to clarify toxicity and outcome after chemotherapy for patients with ALL complicated with Turner's syndrome.

(Internal Medicine 44: 145–148, 2005)

Key words: Turner's syndrome, acute lymphoblastic leukemia, chemotherapy, liver dysfunction, toxicity

Introduction

The association between leukemia and chromosomal instability has been widely reported (1). In particular, children with Down's syndrome have a 10 to 20-fold increase in the risk of developing acute leukemia, which is mainly classified as acute myeloid leukemia (AML) M7 according to the French-American-British (FAB) classification (2). It is well known that these patients occasionally experience severe mucositis and infections by the remission induction and consolidation chemotherapies compared to patients without

Down's syndrome. On the other hand, cases of leukemia that are complicated with Turner's syndrome are extremely rare. Therefore, toxicity and outcome after intensive chemotherapy for patients with acute lymphoblastic leukemia complicated with Turner's syndrome are still unclear.

Case Report

A 17-year-old woman was admitted to our hospital due to general fatigue in May 1999. A peripheral blood examination revealed pancytopenia and she also presented with neck lymph node enlargement and splenomegaly. The patient's white blood cell count was $3.2 \times 10^9/l$ with 23% blasts, the measured hemoglobin level was 6.6 g/dl and the platelet count was $46 \times 10^9/l$. In addition, the patient also had elevated serum levels of aspartate aminotransferase (AST) (129 IU/l), alanine aminotransferase (ALT) (209 IU/l), alkaline phosphatase (ALP) (394 IU/l), γ GTP (326 IU/l) and T-Bil (1.8 mg/dl), but neither serum antibodies against HCV nor the HB antigen were detected. The serum level of albumin, cholinesterase, prothrombin time, and fibrinogen were all within normal range. Bone marrow aspiration revealed that 97.7% of blasts were negative for myeloperoxidase staining. Immunophenotypical analyses also showed that blasts expressed CD10, CD19, CD20, CD34 and HLA-DR but were negative for both CD13 and CD33. Additionally, karyotypical analysis of bone marrow revealed the following abnormalities: 44, XO, der(9)t(3;9)(q11;p13), der(10;19)(q10;p10), del(15)(q15), -16, -19,+22 in 48/50 cells (Fig. 1) and 45, XO in 2/50 cells.

The patient was diagnosed as having acute lymphoblastic leukemia (ALL; L2) based upon FAB classifications. In addition, a diagnosis of Turner's syndrome was made, based on the presence of ovarian dysplasia, abnormal physical features (short stature, lack of pubic hair, a shield-like chest) and a

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Received for publication June 7, 2004; Accepted for publication September 22, 2004

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Figure 1. Karyotypical analysis. Karyotypical analysis was performed using the quinacrine mustard method. Karyotypical analysis of bone marrow revealed the following abnormalities: 44, XO, der(9)t(3;9)(q11;p13), der(10;19)(q10;p10), del(15)(q15), -16, +22 in 48/50 cells. The other two cells had 45, XO.

marked decrease in plasma estrogen levels whereas an intact adrenal-pituitary axis was evident.

She received an induction chemotherapy consisting of daunorubicin (45 mg/m², days 1–3), cyclophosphamide (1,200 mg/m², day 1), vincristine (1.3 mg/m², days 1, 8, 15, and 22), L-asparaginase (3,000 U/m², days 9, 11, 13, 16, 18, and 20), and prednisolone (60 mg/m², days 1–14). On day 17 from the start of chemotherapy, the plasma levels of AST, ALT, ALP, γ GTP and T-Bil elevated to 370 IU/l, 512 IU/l, 1,114 IU/l, 556 IU/l, and 10.1 mg/dl (D-Bil=7.4 mg/dl), respectively. The serum levels of albumin, cholinesterase, fibrinogen, and prothrombin time decreased to 2.9 g/dl, 2,194 mU/ml, 44 mg/dl, and 47%, respectively. We therefore discontinued the administration of L-asparaginase (days 18 and 20) and vincristine (day 22). However, the plasma T-Bil level remained high as 19.6 mg/dl on day 32 following chemotherapy. Although the plasma T-Bil level recovered to normal range within 2 months, there were sustained elevated plasma levels of AST and ALT for more than 6 months following treatment. In spite of the severe liver dysfunction, the patient attained complete remission (CR) on day 31 after initial chemotherapy and karyotypical analysis at this stage revealed 45, XO in 20/20 cells. The patient has now maintained CR for more than five years.

Discussion

Turner's syndrome afflicts approximately 50 per 100,000 females (3) and is characterized by abnormal growth, gonadal dysgenesis and infertility. Turner's syndrome has also been associated with a number of other diseases including diabetes mellitus, reduced bone mineral content and liver dysfunction (4). In addition, higher incidences of neurogenic tumors, gynecological tumors, hepatocellular carcinomas and colon cancers have been observed in individuals suffering from this syndrome (5–8). To our knowledge, the incidence of leukemia development associated with Turner's syndrome is rare, with only two cases of ALL (including the present case), four cases of AML, one case of chronic lymphocytic leukemia and two cases of chronic myeloid leukemia reported to date (9–16) (Table 1).

Takeshita et al (16) have reported that leukemogenesis of CML is dependent upon abnormalities in the sex chromosomes of patients with a 45XO/46XX mosaic. However, in patients with Turner's syndrome, it is unclear whether monosomy X plays an important role in leukemogenesis. Furthermore, in this case study, the patient had karyotypical abnormalities including t(3;9)(q11;p13). Although abnormalities at 3q11 have been observed in lymphoid neoplasms (17), this specific translocation has not been reported

Table 1. Leukemia Complicated with Turner's Syndrome

Reference No. (year)	Disease (FAB subtype)	Age	Extramedullary involvement	Karyotypic analysis of		Therapy	Survival
				normal cells	leukemia cells		
9 (1963)	AML (UE)	64	–	45, XO/47, XXX	UE	PSL, 6-MP	DOD (4 months)
10 (1967)	CLL	62	UE	45, XO/46, XX	UE	UE	UE
11 (1970)	AML (UE)	13	Splenomegaly	45, XO	45, XO	UE	UE
12 (1970)	ALL (UE)	20	Splenomegaly	45, XO	UE	*chemotherapy	Alive (6 months+)
13 (1982), 14 (1984)	*CML	52	Hepatosplenomegaly	45, XO/46, XX	45, XO, t(9;22)(q34;q11)	HU, 6-MP *chemotherapy	Alive (60 months+)
15 (1990)	AML (M5b)	37	–	45, XO	46, X, i(Xq)	DNR, AraC, 6-MP	Alive (12 months+)
16 (1999)	CML	27	Hepatomegaly	45, XO/46, XX	45, XO, t(9;22)(q34;q11)	IFN- α	Alive (24 months+)
our case	ALL (L2)	17	Splenomegaly, LN	45, XO	44, XO, der(9)t(3;9)(q11;p13), der(10;19)(q10;p10), del(15)(q15), -16, -19, +22	DNR, CPM, VCR, L-asparaginase	Alive (60 months+)

AML: acute myeloid leukemia, UE: unevaluable, CLL: chronic lymphocytic leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, *CML: CML patient who developed lymphoid blastic crisis, LN: lymph node enlargement, normal cells: normal cells including buccal mucosal smears, PSL: prednisolone, 6-MP: 6-mercaptopurine, *chemotherapy: combination chemotherapy (details are unevaluable), HU: hydroxyurea, *chemotherapy: L15 protocol, DNR: daunorubicin, AraC: cytosine arabinoside, IFN- α : interferon- α , CPM: cyclophosphamide, VCR: vincristine, L-asparaginase, DOD: died of disease.

previously. It is also not yet clear whether this translocation is associated with leukemogenesis in patients with Turner's syndrome.

Another important finding of the present case report was that prolonged liver dysfunction was evident following chemotherapy. It had been previously reported that leukemia patients with Down's syndrome experienced severe side effects, including infections and mucositis, following chemotherapy treatment (18). As described in this report, patients with Turner's syndrome occasionally have the complication of liver dysfunction. The major cause of liver dysfunction is drug-related, especially in the cases who received hormonal therapy. In addition, auto-immunity and obesity-related liver dysfunction has also been observed (4). We speculate that the anti-cancer agents, including L-asparaginase and prednisolone, are causal in the present case. Histopathological features of L-asparaginase-induced liver dysfunction show diffuse steatosis (19). On the other hand, severe liver dysfunction caused by intrahepatic cholestasis has been described in cases of Turner's syndrome (20). Because the clinical data of patients with Turner's syndrome who have received chemotherapy is still limited, the correlation between liver dysfunction after receiving chemotherapy and Turner's syndrome remains unclear. Therefore, it is important to be aware that cancer patients with Turner's syndrome may develop severe liver dysfunction following intensive chemotherapy.

Here, we report an extremely rare case of ALL complicated with Turner's syndrome. The reporting of additional cases may well be of value in clarifying whether the underlying genomic instability has a bearing on the occurrence of leukemia. Although, acute leukemia, suffered as a complication of Down's syndrome, has a good prognosis (21), the

prognosis for leukemia patients with Turner's syndrome is currently unknown. Her five-year duration of continuing CR is relatively short, however, the outcome of a patient with ALL complicated of Turner's syndrome might not be poor. Further investigation for the differences in cellular drug resistance, pharmacokinetics and the growth advantages of residual leukemic cells is necessary.

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