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SECONDARY ACUTE MYELOBLASTIC LEUKEMIA IN A CHILD WITH ACUTE LYMPHOBLASTIC LEUKEMIA TREATED WITH EPIPODOPHYLLOTOXINS*

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SUMMARY: Özbek N, Çetin M, Tuncer AM, Yetgin S. (Hematology Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Secondary acute myeloblastic leukemia in a child with acute lymphoblastic leukemia treated with epipodophyllotoxins. Turk J Pediatr 1995; 37: 279-282.

Etoposide is a semi-synthetic, topoisomerase active podophyllotoxin derivative which frequently causes deletions and rearrangements on chromosomes 11q23 and 11q22. It can cause therapy-related, acute myeloblastic leukemia in patients receiving the drug in a schedule-dependent manner. Here we present a case with acute lymphoblastic leukemia who developed secondary acute myeloblastic leukemia 28 months after the beginning of therapy which contained etoposide on an every-other-week schedule.
Key words: acute lymphoblastic leukemia, etoposide, secondary acute myeloblastic leukemia.

Etoposide (VP-16), a semi-synthetic podophyllotoxin derivative, is a phase-specific drug which blocks cell cycle progression in the late S and early G2 phase and causes single and double-stranded breaks in DNA. This action is due to inhibition of topoisomerase II, an enzyme which reseals the DNA breaks[1]. Etoposide has been used in malignant diseases such as acute lymphoblastic leukemia (ALL), non-Hodgkin's lymphoma and some solid tumors of children. In recent reports, the leukemogenic potential of etoposide has been extensively reviewed[2,3]. This drug frequently causes chromosomal deletions and rearrangements, especially on chromosomes 11q23 and 11q22[4,5]. Mixed lymphoma leukemia (MLL) locus, a unique gene that is associated with both ALL and acute myeloblastic leukemia (AML), is usually fractured as a result of rearrangement of chromosome 11q23[6,7].

In Hacettepe University's Pediatric Hematology Unit, etoposide has been used in modified St. Jude's Total XI protocol (Table I) since 1991 in children with ALL. This is the first case with secondary acute myelocytic leukemia (AML) in three years of follow-up of 151 ALL patients.

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Table I: Modified St. Jude's Total XI Protocol For Patients with Acute Lymphoblastic Leukemia

Remission Induction (6 weeks)			
Prednisolone (Pred)		: 2 mg/kg	p.o d 1-29
Vincristine		: 0.05 mg/kg	i.v d 1, 8, 15, 22
L-Asparaginase		: 200 U/kg	i.vi.m d 3, 4, 6, 8, 10, 12
Daunorubicine		: 1 mg/kg	i.v d 1, 8
Cytosine Arabinoside (Ara-C)		: 10 mg/kg	i.v d 22, 25, 29
Cyclophosphamide		: 10 mg/kg	i.v d 36, 43
VP-16		: 3-6 mg/kg	i.v d 36, 43
Intrathecal therapy (MTX + Ara-C + Pred)			: d 2, 22, 43
Consolidation (2 weeks): High-dose methotrexate (1.5 g/m²) d 50, 57			
Maintenance (120 weeks, repeated every 4 weeks)			
	1st week	VP-16	i.v 300 mg/m²d 1
		Ara-C	i.v 300 mg/m²d 1
	2nd week	Vincristine	i.v 1.5 mg/m²d1
		Prednisolone	p.o 40 mg/m²d 1-7
	3rd week	VP-16	i.v 300 mg/m²d 1
		Cyclophosphamide	i.v 300 mg/m²d 1
	4th week	Methotrexate (MTX)	i.m 40 mg/m²d 1
		6-Mercaptopurin	p.o 75 mg/m²d 1-7

p.o.; per os, i.v.; intravenous, d; day.

Case Report

A $2^1/_2$-year-old girl was admitted to the hospital with complaints of paleness, failure to thrive and restlessness. The physical examination was normal, and neither hepatosplenomegaly nor lymphadenopathy was evident. The patient's initial complete blood count results were as follows: hemoglobin 3.86 g/dl, hematocrit 10%, white blood cell count (WBC) 5300/mm³ and the peripheral smear revealed 94% lymphoblasts with prominent thrombocytopenia. The chest radiogram displayed mediastinal enlargement. The bone marrow aspiration smear revealed 95% of FAB L2 lymphoblasts. In immunophenotypic studies using the peroxidase antiperoxidase technique (PAP), CD19 was 80%, CD34 was 10%, CD14 was 8% positive and CALLA, CD2 and CD33 were negative. PAS was positive and myeloperoxidase was negative. She was diagnosed with high-risk ALL-L2 and given St.Jude's modified total XI protocol Group A. Bone marrow aspiration performed on day 15 was not in remission. Complete remission was able to be achieved at the end of the remission induction therapy. After remission induction, high-dose methotrexate (MTX) and radiotherapy were administered without complication, and maintenance therapy was started. She was doing well

during maintenance therapy except for bronchopneumonia, which was treated successfully. After 28 months of maintenance therapy consisting of etoposide administration every other week she developed bone marrow relapse. The bone marrow smear showed 95 percent of FAB M2-type blastic infiltration. In immunophenotypic studies, CD13 was 100 percent CD33 was 70 percent, CD5 was five percent positive and CALLA, CD19, CD14, Tdt and Gp IIb/IIIa were negative. Myeloperoxidase was positive and PAS was negative. Chromosomal analysis revealed 46 XX genotype with no additional abnormality. A second remission induction protocol with high-dose methylprednisolone, mitoxantrone and cytosine arabinoside (ara-C) was started. Due to sepsis the therapy could not be completed, and her WBC count gradually increased to 112,000/mm^3. She died because of sepsis one and one-half months after the beginning of the second remission induction therapy.

Discussion

Therapy-related AML accounts for up to 20 percent of AML. Its incidence in recent years has increased due to longer survival and more intensive chemotherapy and irradiation protocols. Pui et al.[8] reported therapy-related AML in 13 out of 733 ALL patients. In this series, the cumulative risk of AML was significantly higher in T-cell ALL patients. The same author reported results of 21 secondary AML patients and demonstrated a schedule-dependent rather than dose-dependent relationship to etoposide exposure[3]. Patients receiving weekly or twice-weekly etoposide had a 12.3 percent cumulative risk of acquiring AML compared to 1.6 percent for those patients who receive etoposide on an every-other-week schedule. Cytogenetic abnormalities of chromosomes 11q and 11q22 were frequently detected in this form of disease. Duration of leukemia treatment before second relapse (treatment-leukemia interval) was usually short (mean 33 months) and response to therapy was poor[5]. Secondary AML due to epipodophyllotoxins usually presented with FAB M4 subgroup.

Our patient was diagnosed with secondary AML by morphological and immunophenotypic studies. The treatment-leukemia interval was similar to that associated with etoposide-related AML[5]. The patient's response to therapy was poor. These findings suggested that etoposide could have been the cause of secondary AML in this patient. In our case, we could not detect any cytogenetic abnormality, and the AML subgroup was diagnosed as M2 type. However, in the literature there are cases reported with different types of AML and cases without any cytogenetic abnormality[2]. This is the first case of AML in our unit suspected to be related to etoposide. Our incidence is still lower than that in the literature, but the mean follow-up of ALL patients in this chemotherapy protocol is shorter than the series in the literature.

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