RESEARCH COMMUNICATION

High Frequency of Acute Promyelocytic Leukemia in Northwest Iran

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Abstract

Acute promyelocytic leukemia (APL) or M3 is a subtype of acute myeloid leukemia, according to the French-American-British group classification. High frequencies of APL have been reported previously by many investigators. We here studied AML patients to determine the frequency of APL in Tabriz in northwest Iran. We reviewed 483 AML patients from 1996-2003. M2 and M3 cases accounted for 43.4% and 19.4% of the total, respectively. Our study thus provides further evidence of high frequencies of APL associated with geographical areas. Further studies should now be performed to evaluate genetic and environmental predisposing factors in Iran.

Key Words: Acute promyelocytic leukemia - frequency - Iran

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Introduction

Acute myeloid leukemia (AML) is divided into subgroups that are distinguished by the morphology of the leukemia cells, specific chromosomal aberrations, gene rearrangement patterns, and different clinical courses and response to therapy. Several subtypes of AML are associated with different molecular mechanisms of pathogenesis so it is critically important to define entities to obtain epidemiological clues as to etiology (Douer 2003). Recent studies have focused on international variation, time trends, genetic syndromes, chromosomal abnormalities, environmental exposure, and subgroups defined either demographically or biologically (Bhatia and Robison ,1999).

The French-American-British (FAB) group has classified AML cases into eight subgroups (M0-M7) based on morphological and histochemical characteristics of the leukemia cells (Douer 2003). It is difficult to perform epidemiological studies in AML subtypes classified according to cytogenetic abnormalities owing to the small number of patients within each subgroup. In 1998, the codes for AML subtypes using cytogenetic information were added to the ICD-O-3 coding. It will thus take many years before we will be able to register sufficient numbers of AML patients with documented chromosomal information to allow appropriate epidemiological studies (Douer 2003).

However, the morphological appearance of acute promyelocytic leukemia (APL) cells is very typical, so the recognition of APL cases is easy with a very low risk of error when using morphology alone(Douer 2003). We here performed a retrospective study of AML patients from 1996-2003 in our hospital, the only referral hospital of hematology oncology in the northwest of Iran, with adult patients refered from Kordestan, West and East Azarbaijan, Ardabil and Zanjan provinces.

Methodology

A cross sectional study was conducted with review of peripheral smears, bone marrow aspiration smears and biopsy and some immunophenotyping reports from 1996-2003 with demographic findings. No cytogenetic findings were available. All patients were classified morphologically and APL was diagnosed with the FAB criteria of APL.

Results

We diagnosed 483 patients with AML in the period, with an age range of 31-60. 70% were from East Azarbaijan, 20% from West Azarbaijan, 5.2% from Kordestan, 4% from Ardabil and 0.8% from Zanjan. The most prevalent subtype was M2 with 43.4% and M3 with 19.4%. The others were M1: 4.9 %, M4: 14.6 %, M5 :0.4% . Table 1 summarizes data for frequency of AML and subtypes in the study period.

Discussion

APL is a clonal expansion of promyelocytic leukemia cells

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Table 1. Frequency of AML subtypes in 1996-2003

Year	AML	M1	M2	M3	M4	M5-M0	unknown
96	60	5	23	17	9	0	4
97	55	1	23	8	12	1	10
98	45	1	20	8	8	0	8
99	54	0	22	12	10	1	9
00	64	5	27	12	4	1	15
01	77	9	33	16	13	1	5
02	75	2	35	13	7	1	17
03	53	1	27	8	8	0	9
Total	483	24	210	94	71	5	
	77%	4.9	43.4	19.4	14.6	0.4	

defined in the FAB classification as M3, and characterized by a translocation between chromosomes 15 and 17, which occurs in 99% of cases and is found only in APL (Douer 2003). Because of this translocation, the nuclear retinoic acid receptor-α (RAR- α) gene from chromosome 17 fuses with the APL gene on chromosome 15, forming a PML/RAR-α fusion transcript (Douer et al,1996). The PML/RAR-α fusion protein gene is known to be involved in the pathogenesis of APL (Douer 2003) and has three subtypes based on the breakpoint site: long (bcr1),short (bcr3) and variable (bcr2) (Santillana et al, 2003). Variant translocations,t(11;17) or t(5;17), have been very rarely described in APL and involve translocation of the RAR-α gene to the PLZF gene or to a nucleophosmin gene on chromosomes 11 and 5, respectively (Douer et al,1996). Several large cooperative group studies have demonstrated a 5% to 13% incidence of APL among accrued AML patients (Douer et al,1996). A similar rate for APL has been reported in several series of cytgenetic analyses of AML patients from various geographic locations (Douer et al,1996). A 23% prevalence of M3 was found on analysis of 86 AML patients diagnosed at the Los Angeles County-University of Southern California Medical Center between 1987 and 1991. This center has high proportion of patients of Latino origin. They described the high frequency of AML M3 (40%) among Latino AML patients (Douer et al,1996). Several small series from different countries in Central and South America and Africa have previously noted a higher-than-expected frequency of APL in pediatric AML patients (Douer et al,1996). According to Pulsoni et al (1998) a high proportion of APL with respect to other AML subtypes in the north east of Italy exists in comparison with the rest of the country, along with a younger age of APL patients compared to the other AMLs. APL cases were also relatively young in another study of AMLs (Mele et al,1995). Differences were noted in an epidemiologic study on 256 cases of APL in Italy (Avvistati et al,1991). Estey et al (1997) further described more frequent APL in Latinos and younger patients. Our APL patients accounted for 19.4 % of the total AML cases. Our study and others suggest a genetic predisposition or environmental predisposing factor toward APL in certain geographical areas. Regardless, certain races may be more prone to chromosomal breakage at a site involved in the t(15:17) translocation.

In fact, more limited steps of chromosomal mutations may be required for leukemic transformation to APL, in contrast to other forms of AML (Douer et al,1996). If further studies in other centers in Iran support our findings, it would be interesting to determine whether a specific genetic background is involved. Although much is known about risk for treatment-related leukemias in adults, environmental, occupational, and other risk factors are less well studied (Sandler et al,1997). The high frequency of APL in Northwest Iran might be related to environmental factors and exposure to carcinogens in the diet. Chinese are reported to demonstrate an association between APL and bimolane, a drug used in China to treat psoriasis (Douer et al,1996). The rate of bcr1 among APL patients originating in Latin America was 75% while it was only 50-55% in non-Latinos in the USA (Douer et al,1996). The particular breakpoint site of the PML gene might be associated with an etiology that may be determined genetically (Douer et al,1996). Is this true in Iran? Further studies are clearly warranted for evaluation of risk factors and genetic findings for APL in Iran.

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