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3q21 and 3q26 cytogenetic abnormalities in acute myeloblastic leukemia: biological and clinical features

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ABSTRACT

Background and Objective. **Acute myeloblastic leukemia (AML) with features of myelodysplastic syndrome (MDS) and abnormalities of megakaryocytopoiesis is often characterized by cytogenetic aberrations of the 3q21 and 3q26 bands involving inv(3)(q21q26) and (3;3)(q21;q26). These aberrations have been described in all FAB subtypes with the exception of M3, and in MDS and in megakaryoblastic crisis of chronic myeloid leukemia. We reviewed the biological and clinical features of 10 cases of AML with inv(3)(q21q26) and t(3;3)(q21;q26).**

Design and Methods. **Four hundred and sixteen patients with AML were studied in our Institute by cytogenetic analysis and 10 (2.4%) showed inv(3)(q21q26) (7 patients) or t(3;3)(q21;q26) (3 patients): 7 males, 3 females; median age, 43.5 yrs. We also used RT-PCR to investigate the pattern of expression of the EVI-1 gene in 5 patients.**

Results. **Additional chromosomal changes were demonstrated in 6 patients. In 5/10 cases a preceding MDS had been observed. A possible occupational exposure was established in 2 patients (a farmer and an histologist employing organic solvents) and another patient had a therapy-related leukemia. AML subtype was M1 in 9 patients and M2 in 1. A variable excess of micromegakaryocytes was observed in all the patients. In 5 patients the platelet count was normal or increased (median number: 172.5×10^9/L; range 55-440). Expression of EVI-1 gene was present in all the 5 patients studied. The clinical course and outcome was extremely poor: 9/10 patients were resistant and 1 patient showed a partial remission after induction therapy. Of the 9 patients resistant to the first line chemotherapy, 7 were also resistant to the second line chemotherapy. Three patients obtained a morphologic complete remission after third line chemotherapy (duration 1, 3 and 6 months); 2 of them were submitted to autologous bone marrow transplantation, but relapsed after 1 and 3 months. The median overall survival was 5.5 months.**

Interpretation and Conclusions. **Our findings evidence a strong correlation between 3q21q26 chromosomal aberrations, abnormalities of megakaryocytopoiesis and lack of response to conventional chemotherapy and support the diagnostic and prognostic relevance of chromosome characterization in the classification of AML.**

Key words: cytogenetics, 3q abnormalities, acute myeloblastic leukemia, EVI-1 expression, myelodysplastic syndrome

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Specific aberrations involving 3q21 and 3q26 have been demonstrated in all but one (M3) of the subtypes of acute myeloblastic leukemia (AML).[1-8] These abnormalities have also been shown to occur in myelodysplastic syndrome (MDS) and in the megakaryoblastic crisis (BC) of chronic myeloid leukemia (CML).[9,10] Almost all these hematologic diseases are characterized by morphologic abnormalities of thrombopoiesis such as the presence of micromegakaryocytes (MM) in the bone marrow (BM), normal or elevated platelet counts, minimal or no response to chemotherapy and a poor prognosis.[4,6-7] Major abnormalities of 3q, including a paracentric inversion [inv(3)(q21q26)] and a translocation between the long arms of both homologous chromosomes 3 [t(3;3)(q21;q26)], were first described in AML patients by Bernstein *et al.*[11] and by Rowley and Potter.[12] However, these chromosome abnormalities are relatively infrequent in AML (0.5% to 2%) and have been reported mostly as single case descriptions or in reviews of multiple case reports from different Institutions.[5,13] Out of 416 AML patients studied in our Institute by cytogenetic analysis, we found an inv(3)(q21q26) in 7 cases and a t(3;3)(q21;q26) in 3 cases (2.4%).

We reviewed the biological and clinical features of these patients and their response to therapy.

Design and Methods

Patients

Four hundred and sixteen patients with AML were studied in our Institute by cytogenetic analysis: 32 cases were secondary to other tumors and 60 cases had a preceding MDS (22.1%). Ten patients (2.4%) showed inv(3)(q21q26) or t(3;3)(q21;q26). The diagnosis was made according to FAB criteria. Clinical features of the patients are shown in Table 1.

Cytogenetic studies

Cytogenetic analyses were performed at diagnosis on bone marrow (BM) from all the patients as reported elsewhere.[14] The karyotyping and G-banding with Wright's stain were performed after a short-term culture (24-48 hours) with no stimulation. Chromosomes were classified according to the *International System for Human Cytogenetic Nomenclature*.[15] The number of metaphases analyzed for each patient ranged from 10 to 23 (median number 18.5). Five patients were studied at different stages of chemotherapy (2 to 6 studies for each patient), to evaluate their disease follow-up.

Fluorescent in situ hybridization studies

A fixed cell suspension stored at 4°C was used for a fluorescent *in situ* hybridization (FISH) study in patient #6 who carried a monosomy 7 besides t(3;3). A Spectrum Green CEP #7 α-satellite (Vysis) was used to detect the abnormal cells. The cells were analyzed by fluorescent microscopy with a double pass filter (PI-FITC). Five hundred nuclei were scored. Control samples were also analyzed. The cut-off for recognizing monosomy 7 was set at 5% of interphase cells showing 1 well-delineated signal, according to our control's values.

Detection of ecotropic virus integration site 1 RNA

RNA was extracted from primary specimens as described.[16] Ecotropic virus integration site 1 (EVI-1) RNA was detected by RNA polymerase chain reaction (PCR) as previously described in detail[17] and visualized using ethidium bromide-stained agarose gels.[18] Primer sets were employed spanning sequences from bp 2361 to 2390 and bp 2110 to 2139 (sense primer 5'-ACTGACTGTAAGAGCTCACTGGCCTCAGGT-3', antisense primer 5'-AGCAACGTCGAATCAAGACCT-GCTTGAGAT-3') of the coding sequence. The 3' primers detect alternatively spliced transcripts and give rise to two bands in most preparations as previously described in detail.[17] Primers detecting ABL RNA were used as controls.[19] RNA from a patient with typical 3q21q26 served as a positive control and RNA from the NB4 cell line as a negative control for EVI-1 RNA. The EVI-1 PCR products were identified by probing restriction digestion with Hind III enzyme and verifying fragments of expected size on agarose gel separation.

Results

Table 1 shows the clinical and morphologic features at diagnosis of the 10 patients (7 males and 3 females; median age 43.5 yrs; range 24-59 years). At the time of cytogenetic analysis all patients presented with AML. AML of FAB-subtype M1 was diagnosed in 9 patients. Only 1 patient (#3) was classified as having M2.

Altered megakaryocyte development, characterized by an excess of dysplastic and hypolobulated forms (MM) was demonstrated in all patients. Platelet counts ranged from 55 to 440×10^9/L (median 172.5×10^9/L). Counts were normal or increased (#1) in 5 cases, and decreased in the other 5 cases. Dysplastic erythropoiesis and/or granulocytopoiesis was observed in 8 patients. A preceding symptomatic MDS could be established in 3/4 (75%) patients with t(3;3) and in 2/6 (33.3%) patients with inv(3). In only 2 patients (#7 and #8) was the karyotype during the MDS phase available and in both showed the same abnormalities as during the overt AML phase. The duration of the MDS phase was brief in 4 cases (2 months in 3 patients and 4 months in 1 patient). Case #5 developed an overt AML 11 months after

Table 1. Morphologic and clinical features of patients at diagnosis.

Pts.	Sex/age	Hb g/L	WBCx10^9/L	%BC	Plt x10^9/L	Preceding MDS	Exposure to mutagens	FAB	MMK	Dysgran	Dyseryth
1	M/55	6.9	6.8	5	440	RAEB	pesticides	M1	+++	++	++
2	M/24	7.1	23.7	21	55	no		M1	+++	+++	+++
3	F/45	9.8	59.0	50	304	no		M2	++	–	–
4.	M/42	8.6	13.3	19	225	no		M1	+++	++	+
5.	F/59	7.2	18.7	30	72	RA	organic solvents	M1	++	+	+
6	M/52	6.4	2.1	28	142	RAEB–T		M1	+++	++	+++
7	M/50	8.3	2.4	50	266	RAEB		M1	+++	–	–
8	F/41	9.6	17.1	53	203	RAEB–T		M1	++	+	+
9	M/42	11.1	20.4	60	64	no	preceding chemotherapy*	M1	+++	+++	+++
10	M/36	4.7	1.3	19	92	no		M1	+++	+	++

*MDS: myelodysplastic syndrome; RAEB: refractory anemia with excess of blasts; RAEB-T: RAEB in transformation; MMK: micromegakaryocytes. *methotrexate-cisplatin-adriamycin-ifosfamide. += present; ++= moderate; +++= marked; -= absent.*

Table 2. Cytogenetic and molecular studies of the patients at diagnosis.

Pts.	% abnormal metaphases	karyotype	EVI-1 expression
1	100	46,XY,t(3;3)(q21;q26)(30%)/ 46,XY,t(3;3)(q21;q26),ins(13q)(70%)	N.D.
2	64	45,XY,inv(3)(q21q26),-7	N.D.
3	100	46,XX,inv(3)(q21q26)	+
4	100	45,XY,inv(3)(q21q26),-7	+
5	100	46,XX,t(3;3)(q21;q26)	N.D.
6	86	45,XY,t(3;3)(q21;q26),-7	+
7	100	46,XY,inv(3)(q21q26)	N.D.
8	90	46,XX,inv(3)(q21q26)	N.D.
9	96	45,XY,inv(3)(q21q26),-5,del(7)(q22q34)	+
10	83	45,XY,t(3;3)(q21;q26),-7	+

N.D.: not done; +:positive.

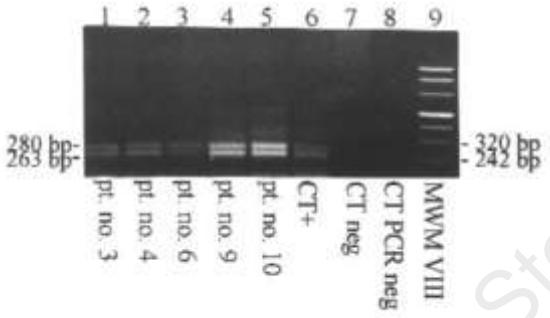

Figure 1. EVI-1 expression in t(3;3) and inv(3) positive patients detected by RNA PCR. Lanes 1-5 represent the molecular studies of patients 3, 4, 6, 9 and 10, respectively. Lanes 6 and 7 are positive and negative controls (CT) for EVI-1 expression, respectively. Lane 8 shows CT PCR reaction. Lane 9 represents molecular weight marker VIII from Boehringher Mannheim. Molecular weights of expected EVI-1 bands of 280 bp and 263 bp are shown.

the diagnosis of MDS. An antecedent exposure to mutagens was possible in 3 cases: patient #1 was a farmer employing pesticides; patient #5 was a biochemistry worker employing phenol-based substances; patient #9 had been previously treated for a primary tumor with several courses of chemotherapy including methotrexate, cisplatin, adriamycin, and ifosfamide plus radiotherapy.

The inv(3)(q21q26) or t(3;3)(q21;q26) was the sole abnormality in 4/10 patients (cases #3, 5, 7 and 8). Patients #2, 4, 6 and 10 showed a monosomy 7, while patient #9 had a complex karyotype involving monosomy 5 and del(7)(q22q34) in all observed metaphases, and patient #1 an ins(13q) in 70% of the cells. Metaphases with a normal karyotype were sporadically observed in patients #2, 6, 8, 9 and 10 (Table 2). We also investigated the expression of human EVI-1 gene in 5 patients using a reverse transcription (RT)-PCR approach (Table 2). We detected EVI-1 expression in all 5 patients (Figure 1).

All patients received chemotherapy as shown in Table 3. Clinical course and outcome was extremely poor: 9/10 patients were resistant to the first course of induction chemotherapy, and 6/10 patients died within 9 months of diagnosis of AML; only one patient (#10), with a follow up of 10 months, was still alive after allogeneic BM transplantation (BMT). Three patients achieved complete clinical and cytologic remission (CCR) (#4-6), but subsequently relapsed. However, patient #5 showed inv(3;3) in 2 out of 50 observed cells in the autologous BM collected during CCR and patient #6 showed 9% of cells with monosomy 7 when FISH was done in cytogenetic CCR.

Discussion

The incidence of 3q chromosomal abnormalities in AML remains rather unclear. The frequency of 3q21q26 abnormality ranges from 0.5 according to the *Fourth International Workshop on Chromosomes in Leukemia*[20] to 3.4% as reported by Fonatsch *et al.* on behalf of the German group.[6] We found 3q abnormalities in 2.4% of all cases of AML cytogenetically studied in a single center. Previous studies have underlined the strong correlation between the abnormality involving 3q21 and 3q26 bands and trilineage myelodysplasia with prominent presence of micromegakaryocytes.[1-4,7,9] The association between thrombocytosis and 3q abnormalities is generally considered less strong.[7] However, all our patients had dysmegakaryopoiesis in the BM, often accompanied by dyserythropoiesis and dysgranulopoiesis, and 50% had platelet counts >150×10^9/L. Abnormal multilineage hematopoiesis (i.e. abnormal megakaryopoiesis, erythropoiesis and granulopoiesis) suggests involvement of multipotent stem cells,[8] as does the presence of 3q21q26 abnormalities in all FAB subtypes (except M3), MDS, BC of CML, polycythemia vera (PV) and myelofibrosis with myeloid metaplasia (MMM).[9,10]

Since in previous studies inv(3) or t(3;3) has rarely been described in *de novo* cases of AML, 3q21q26 chromosomal abnormalities may be characteristic of secondary AML.[6] In 6/10 of our patients a symptomatic MDS prephase and/or mutagen exposure was established, in line with the high frequency of secondary leukemia found by other authors,[1,3] and the brief duration of the MDS phase has already been described in cases of AML following MDS with t(8;21)(q22;q22).[21] However, 4/10 of our patients presented with *de novo* AML.

Abnormalities of chromosomes 5 and 7 are frequently associated with secondary leukemias.[3, 6,22,23] We found such aberrations in 5/10 of our patients, 3/5 of whom had *de novo* AML. Due to the low number of cases, no correlation could be made between these additional aberrations and age and/or median

Table 3. Therapy and outcome of the patients.

Pts.		Chemotherapy regimen	Response	DFS (mos.)	OS (mos.)
1	I line	3-7 dauno-ARAC	Res	0	5
	II line	Bisantrene 7d	Res		
2	I line	3-7 dauno-ARAC	Res	0	4
	II line	MEC6	Res		
3	I line	REES	Res	0	21
	II line	FLA+G	Res		
4	I line	REES	Res	6	16
	II line	ICE like	Res		
	III line	FLA+G	CR		
		ABMT	CR		
5	I line	FLA+G	PR	3	9
	II line	FLA+G	PR		
	III line	ARA-C x2	CR		
		ABMT	PR		
6	I line	ICE	Res	1	17
	II line	FLAN	PR		
	III line	FLAN	CR		
	IV line	FLAN	CR*		
7	I line	FLAN	Res	0	2
	II line	ICE	Res		
8	I line	ICE	Res	0	1
9	I line	FLAN	Res	0	6
	II line	FLAN	Res		
10	I line	ICE	Res	0	10+
	II line	3-7+ PSC833	Res		
		BMT	CR		

CR: morphologic complete remission, but not confirmed by FISH studies 3-7 dauno-araC: daunomycin (60 mg/m²/day, days 1-3) and cytosine arabinoside (200 mg/m²/day, days 1-7); MEC6: etoposide (80 mg/m²/day), cytosine arabinoside (1 g/m²/day), mitoxantrone (80 mg/m²/day) for 6 days; REES: daunomycin (50 mg/m²/day, days 1-3-5), cytosine arabinoside (100 mg/m²/12 hours, for 5 days), vepeside (100 mg/m², for 5 days); FLAN: fludarabine (30 mg/m²/day for 5 days), cytosine arabinoside (2 g/m²/day for 5 days) and mitoxantrone (6 mg/m² for 3 days); FLAG: fludarabine (30 mg/m²/day for 5 days), cytosine arabinoside (2 g/m²/day for 5 days) and G-CSF 5 mg/kg/die from day –1 of the chemotherapy until the number of PMN reach 500/mm³. BMT: bone marrow transplantation; ABMT: autologous BMT; ICE: idarubicin (10 mg/m²/day, days 1-3-6), etoposide (100 mg/m²/day for 5 days), cytosine arabinoside (100 mg/m²/day, continuous infusion for 10 days); PSC833: modulator of multidrug resistance.*

survival. It should be noted that patient #9 had been treated with several agents including a topoisomerase II inhibitor. Involvement of band 3q26 has previously been associated with therapy-related AML in patients treated with combination chemotherapy involving targeting DNA topoisomerase II.[24]

Our series contained a striking predominance of males, as did that of Jenkins *et al.*[3] but not those of several other authors.[2,4,6] Therefore, molecular characterization of specific genes on the breakpoints in 3q21 and 3q26 that may play a fundamental role in normal maturation and differentation of hematopoietic progenitor cells and also affect the megakaryocyte lineage can be considered an important priority.

The thrombopoietin (TPO) gene maps to human chromosome 3q26. However, previous studies[25,26] have demonstrated that TPO is not deregulated in 3q21q26 syndrome and thus it cannot be held responsible for the stimulated thrombopoiesis observed in these patients. The EVI-1 gene has been cloned and shown to map to the region 3q25-q26.[27] Although it is not expressed in normal hemopoietic cells, aberrant expression of EVI-1 gene has been reported almost exclusively in cases presenting translocations involving band 3q26.[17, 28-33] Of the 5 cases with inv(3) or t(3;3) that we analyzed, expression of the EVI-1 gene was detectable in all, the major transcript being comparable in size to normal EVI-1 transcripts. Our results support the hypothesis that transformation is a consequence of inappropriate expression of the normal EVI-1 gene product.

Our patients showed high rates of resistance (Table 3) to all the different chemotherapeutic approaches used. Nine patients were resistant to the first line of conventional chemotherapy, and their clinical outcome was poor. These results are consistent with those of other authors,[2-4,7] who reported that therapy with cytostatic drugs failed in most cases. In our series, the only CCRs were achieved after three lines of chemotherapy (3 patients) or after allogeneic BMT from an unrelated donor (1 patient). However, in 2/4 of these cases the CCR was not confirmed by cytogenetic/ FISH analyses.

In conclusion, our findings confirm the strong correlation between 3q21q26 chromosomal aberrations, abnormalities of megakaryocytopoiesis and lack of response to conventional chemotherapy, and support the diagnostic and prognostic relevance of chromosome characterization in the classification of AML, as proposed by other authors. In view of the minimal or absent response to conventional or aggressive chemotherapy, patients with inv(3) and t(3;3) should be considered at very high risk.

Contributions and Acknowledgments

NT was responsible for the conception of the study. GB and EO performed the molecular studies and CC, DR and SP performed the cytogenetic studies. NT, GB and GM wrote the paper. The others took part in the study and analysis of the data. ST was the senior author. Otherwise the criteria applied for the order of the authors was the degree of their contribution to the study.

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Disclosures

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