Biological and clinical features of T-biphenotypic acute leukaemia: report from a single centre

We read with interest the work from Rubio *et al* (2003) on adult T-biphenotypic leukaemia, reporting the clinical and biological characteristics of this rare clinical entity. We have reviewed our file of acute leukaemias, both lymphoblastic and myeloid, to identify the biphenotypic acute leukaemias (BAL) and, among them, the cases co-expressing T-lymphoid and myeloid markers.

In the last 10 years (1993–2003), we have diagnosed 280 acute leukaemias, 202 myeloid (AML) and 78 lymphoblastic (ALL). Using the diagnostic criteria recently proposed (Bene *et al*, 1995), 26 (9%) patients had a BAL. In accordance with other reports (Legrand *et al*, 1998; Killick *et al*, 1999), the most common BAL phenotype consisted of the co-expression of myeloid and B-lymphoid markers, but three of these patients (11·5%) had a T-BAL.

Clinical and biological characteristics of the patients are listed in Table I. Two of the patients were female and one was male. The median age at diagnosis was 58 years (range 26–60 years). According to the French–American–British (FAB) classification, all the patients had a type 2 ALL, with co-expression of myeloid markers, with a score of at least two for both T-lymphoid and myeloid markers. Cytogenetic analysis was available for two patients. Both showed a deletion of chromosomes 7 and 12, plus other abnormalities; no Philadelphia chromosome (Ph+) metaphases were documented. When karyotype was missing, *BCR-ABL* transcripts were not detected by molecular biology. We analysed the multidrug-resistance (MDR) proteins and found an overexpression of P-glycoprotein with a mean of 7·2 (range 6·6–8·1), while lung resistance-related protein and multidrug resistance-related protein 1 were normally expressed.

Two patients (patients 2 and 3) received an ALL-designed induction therapy (vincristine, idarubicin, prednisone and asparaginase). Patient 2 died during induction due to a haemolytic-uraemic syndrome and pneumonia. Patient 3 achieved a complete remission (CR) that was consolidated with two courses of therapy (high-dose cytarabine, then vincristine, methotrexate, cyclophosphamide and adriamicin). She relapsed after 5 months but attained a second CR with salvage therapy (liposomal daunorubicin and high-dose cytarabine). The remission lasted for another 4 months, then the patient relapsed again and died of cerebral haemorrhage.

Patient 1 displayed a more undifferentiated morphology, with two blast populations. He initially received an AML-like course with idarubicin and low-dose cytosine arabinoside. Day +14 bone marrow was still completely blastic, but with more distinctive lymphoid features. He therefore was switched to our ALL protocol, attaining a CR and subsequently underwent an autologous bone marrow transplant. He is alive in CR, 9 years after transplant.

Our small experience partially confirms the findings of Rubio *et al* (2003). In addition, our patients were morphologically classified as L2 and presented superficial adenopathies at diagnosis, but none of them had mediastinal involvement. Leucocytosis and peripheral blast count were generally low or moderate. None of our patients had the Philadelphia chromosome or *BCR-ABL* rearrangement, but two cases displayed unfavourable cytogenetics, with deletions of chromosome 7. In a previous report, four of six patients with T-BAL had a complex karyotype and none was Ph+ (Carbonell *et al*, 1996).

Treatment of BAL remains controversial and these patients have generally a bad prognosis. Except in patient 2, who died during induction, we observed a good response when a mixed or 'sequential' AML/ALL induction therapy was used, possibly followed by intensification with transplantation. When an ALL-type course was used alone (patient 3), a CR was obtained but it was short-lived, and also a salvage therapy with high-dose cytarabine and liposomal daunorubicin was only

Table I. Clinical and biological characteristics of patients with T-biphenotypic acute leukaemia.

No.	Age (years)	Sex	FAB	WBC (10^9/l)	Blast (%)	Tumour location	Karyotype	*BCR/ABL*	My. score	T-ly. score
1	26	M	L2	1·2	24	Superficial + spleen	Failure	Neg.	2·0	2·5
2	60	F	L2	77·0	100	Superficial	40–45,XX,del(7),−12, +mar (10/15)	N/A	2·0	2·0
3	58	F	L2	12·3	73	Superficial	46,XX,del(7),del(11), del(12),dup(13)	N/A	2·0	3·0

M, male; F, female; FAB, French–American–British classification; WBC, white blood cell; N/A, not available; My. score, myeloid score; T-Ly. score, T-lymphoid score.

transiently effective. The aggressive clinical course of T-BAL may be associated with adverse cytogenetic abnormalities and MDR overexpression, but these speculations require confirmation in larger studies.

Mario Tiribelli
Daniela Damiani
Paola Masolini
Anna Candoni
Elisabetta Calistri
Renato Fanin

Division of Hematology and Bone Marrow Transplantation, University Hospital, Udine, Italy. E-mail: mtiribelli@hotmail.com

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Association of the 1513C polymorphism in the P2X7 gene with familial forms of chronic lymphocytic leukaemia

B-cell chronic lymphocytic leukaemia (CLL) is unique in showing a threefold increased incidence in closely related family members compared with other lymphoproliferative diseases (Houlston *et al*, 2003). A candidate gene for this familial incidence is the P2X7 gene, which codes for a cytolytic receptor, activated by extracellular ATP. We have identified a loss-of-function single nucleotide polymorphism (1513 A→C) in the P2X7 gene and reported an increase in frequency of this polymorphic allele in 36 patients with CLL (Wiley *et al*, 2002). In contrast, other recent reports did not find any difference in the frequency of this polymorphic allele between normal and CLL subjects (Starczynski *et al*, 2003; Zhang *et al*, 2003).

To further explore the involvement of the P2X7 as a susceptibility gene in CLL, we expanded our previous study to include 42 cases of familial and 74 cases of sporadic CLL. A total of three intergenerational pairs and six sibling pairs and eight single familial cases (affected relatives unavailable for study) were recruited from Eastern Australian centres. DNA samples from an additional five parent-child and three sibling pairs were obtained from the UK, courtesy of Dr D. Catovsky. Normal subjects of Western European descent ($n = 411$) with no history of haematological disease were recruited from the partners of patients or staff from our institutions. As expected, the median age at diagnosis was lower in familial CLL than for the sporadic CLL cohort (Table I). However, there were no significant differences in the IgV_H mutational status or stage at diagnosis between familial and sporadic CLL (Table I).

Table I. Clinical and molecular characteristics in patients with familial and sporadic chronic lymphocytic leukaemia (CLL).

	Familial CLL ($n = 42$)	Sporadic CLL ($n = 74$)	All cases ($n = 116$)	*P*-value
Median age, years	56·1	65·2	62·5	<0·001*
Median follow-up time, years	5·5	4·5	4·7	
V_H gene mutation				
Unmutated	7	15	22	
Mutated	14	46	60	0·510†
Stage at diagnosis‡				
A(0)	21	49	70	
A(I), B, C	4	24	29	0·091†

*Familial *versus* sporadic CLL using Mann–Whitney *U*-test non-parametric comparison.
†χ^2-test.
‡According to Binet stage.