bjh short report

Prognostic heterogeneity of adult B-cell precursor acute lymphoblastic leukaemia patients with t(1;19)(q23;p13)/*TCF3-PBX1* treated with measurable residual disease-oriented protocols

Jordi Ribera,[1] Isabel Granada,[1] Mireia Morgades,[1] Teresa González,[2] Juana Ciudad,[3,4] Esperanza Such,[5] María-José Calasanz,[6] Santiago Mercadal,[7] Rosa Coll,[8] José González-Campos,[9] Mar Tormo,[10] Irene García-Cadenas,[11] Cristina Gil,[12] Marta Cervera,[13] Pere Barba,[14] Dolors Costa,[15] Rosa Ayala,[16] Arancha Bermúdez,[17] Alberto Orfao[3,4] and Josep-Maria Ribera,[1] on behalf of the Programa para el Tratamiento de Hemopatias Malignas (PETHEMA) Group (Spanish Society of Hematology, SEHH)

[1]Josep Carreras Leukaemia Research Institute, ICO-Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, [2]Hospital Universitario de Salamanca, Universidad de Salamanca, IBMCC (CSIC/USAL), IBSAL and CIBERONC, [3]Cytometry Service (NUCLEUS) and Department of Medicine, Cancer Research Center (IBMCC-CSIC/USAL-IBSAL), University of Salamanca, Salamanca, [4]Centro de Investigación Biomédica en Red de Cáncer (CIBER-ONC) CB16/12/00400, Instituto de Salud Carlos III, Madrid, [5]Hematology Department, Hospital Universitari Politècnic La Fe, Valencia, [6]Centro de Investigación Clínica Aplicada (CIMA), Universidad de Navarra, Pamplona, [7]Hematology Department, ICO-Hospital Duran i Reynals, Hospitalet de Llobregat, [8]Hematology Department, ICO-Hospital Josep Trueta, Girona, [9]Hematology Department, Hospital Universitario Virgen del Rocío, Sevilla, [10]Hematology Department, Hospital Clínico Universitario, Valencia, [11]Hematology Department,

Summary

The prognosis of t(1;19)(q23;p13)/transcription factor 3-pre-B-cell leukaemia homeobox 1 (*TCF3-PBX1*) in adolescent and adult patients with acute lymphoblastic leukaemia (ALL) treated with measurable residual disease (MRD)-oriented trials remains controversial. In the present study, we analysed the outcome of adolescent and adult patients with t(1;19)(q23;p13) enrolled in paediatric-inspired trials. The patients with *TCF3-PBX1* showed similar MRD clearance and did not have different survival compared with other B-cell precursor ALL patients. However, patients with *TCF3-PBX1* had a significantly higher cumulative incidence of relapse, especially among patients aged ≥35 years carrying additional cytogenetic alterations. These patients might benefit from additional/intensified therapy (e.g. immunotherapy in first complete remission with or without subsequent haematopoietic stem cell transplantation).

Keywords: acute lymphoblastic leukaemia, adults, t(1;19)(q23;p13)/*TCF3-PBX1*, prognosis, cytogenetic alterations.

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Hospital de Sant Pau, Josep Carreras Leukaemia Research Institute, Barcelona, [12]*Hematology Department, Hospital General de Alicante, Alicante,* [13]*Hematology Department, ICO-Hospital Joan XXIII, Tarragona,* [14]*Hematology Department, Hospital Universitari Vall d'Hebrón,* [15]*Haematopathology Section, Department of Pathology, Hospital Clínic, Barcelona,* [16]*Hematology Department, Hospital Universitario Doce de Octubre, Madrid, and* [17]*Hematology Department, Hospital Universitario Marqués de Valdecilla, Santander, Spain*

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Correspondence: Jordi Ribera, Josep Carreras Leukaemia Research Institute, ICO-Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Carretera de Canyet s/n, Camí de les Escoles s/n, 08916 Badalona, Spain.
E-mail: jribera@carrerasresearch.org

Introduction

The t(1;19)(q23;p13)/transcription factor 3-pre-B-cell leukaemia homeobox 1 (*TCF3-PBX1*) is a subtype of B-cell precursor acute lymphoblastic leukaemia (BCP ALL) with an incidence of around 5–7%.[1] In paediatric ALL, therapy intensification has improved the outcome, moving from poor to intermediate–good prognosis. In adults the scenario is less clear, with reports showing favourable,[2] intermediate[3–5] and poor prognosis.[6–8] The low incidence of this alteration limits the prognosis assessment in homogeneously treated patients, and differences within chemotherapy schedules and in the indication of allogeneic haematopoietic stem cell transplantation (alloHSCT) may explain these controversial results. However, the prognostic significance of *TCF3-PBX1* in paediatric-inspired, measurable residual disease (MRD)-based trials has not been extensively evaluated in adolescents and adults with ALL.

Patients and methods

The outcomes of adolescent and adults (aged 15–60 years) with Philadelphia (Ph) chromosome-negative BCP ALL and *TCF3-PBX1* rearrangement diagnosed between 2003 and 2017 and treated with MRD-oriented protocols from the Programa Español de Tratamientos en Hematología (PETHEMA) Group (high-risk protocols ALL AR03 and ALL HR11, and standard-risk protocol ALL RE08) were retrospectively analysed.[9–11] Patients were re-classified into cytogenetic subtypes according to the World Health Organization (WHO) 2017 classification. When possible, patients with normal karyotype or no metaphases were screened for the most recurrent BCP ALL subtypes, including *TCF3-PBX1*, by fluorescence *in situ* hybridisation (FISH) and by reverse transcription polymerase chain reaction to a lesser extent. Among patients with Ph-negative ALL, high-risk was defined by age of >30 years, white blood cell (WBC) count of $>30 \times 10^9$/l or the presence of 11q23/Lysine Methyltransferase 2A (*KMT2A*) rearrangements. Therapeutic decisions were based on MRD levels in the two high-risk protocols. A good MRD response was considered when the MRD level was <0·1% at the end of induction and <0·01% at the end of consolidation. Patients with end-consolidation MRD levels of ≥0·01% received alloHSCT, while patients with good MRD clearance received delayed consolidation and maintenance therapy. MRD was centrally assessed by multiparametric flow cytometry in a EuroFlow laboratory. Comparisons between groups were performed with the chi-square test, Fisher's exact test and the median test as appropriate. Overall survival (OS) was estimated using the Kaplan–Meier method and curves were compared by the log-rank test. The cumulative incidence of relapse (CIR) was calculated using cumulative incidence functions considering non-relapse mortality (NRM) as a competing risk and was compared by Gray's test. Two-sided $P < 0{\cdot}05$ were considered statistically significant.

Results

Of 539 patients with BCP ALL, 154 were excluded for uninformative cytogenetics. From 385 patients with Ph-negative

BCP ALL with informative cytogenetics, 26 (7%) were classified as *TCF3-PBX1*. Of them, 22 had t(1;19)(q23;p13) or der(19)t(1;19) by G-banding and four cases with normal karyotype (two) or no metaphases (two) showed *TCF3-PBX1* rearrangement by FISH. Patients with t(1;19) were classified according to the type of rearrangement [balanced translocation *versus* der(19)t(1;19)] and the karyotype complexity [isolated t(1;19)/der(19)t(1;19) *versus* t(1;19)/der(19)t(1;19) with additional chromosomal alterations (ACA)]. In all, 10/22 (45%) patients with *TCF3-PBX1* had t(1;19) balanced rearrangements, while 12/22 (55%) had der(19)t(1;19). In turn, nine of the 22 (41%) cases had a t(1;19) or der(19)t(1;19) as an isolated aberration, while 13/22 (59%) had ACA [median (range) 2 (1–10)]. The most recurrent ACA were trisomy 1/1q (four), −6/del(6q) [MYB Proto-Oncogene (*C-MYB*); three], del(9p) [cyclin-dependent kinase inhibitor 2A/B (*CDKN2A/B*), paired box 5 (*PAX5*); five] and −13/del(13q) [retinoblastoma 1 (*RB1*); four]. Although der(19)t(1;19) was preferentially seen in association with ACA, there was no statistically significant relationship between both classifications (balanced/derivative *versus* isolated/ACA). Four patients (15%) were treated within the ALL RE08 protocol, while 10 and 12 patients were treated according to the ALL AR03 and ALL HR11 trials respectively.

The main clinical and biological characteristics of the 26 patients with *TCF3-PBX1* were compared with those of the 359 patients with Ph-negative BCP ALL with informative cytogenetics (Table I). The patients with *TCF3-PBX1* showed higher female gender, more frequent pre-B phenotype and a trend towards higher WBC counts. There were no significant differences in age and WBC count between patients with balanced translocation, der(19)t(1;19), isolated t(1;19)/der(19)t(1;19) and t(1;19)/der(19)t(1;19) with ACA. All the patients with *TCF3-PBX1* achieved complete remission (CR). End-induction MRD response (available for 23/26 *TCF3-PBX1* and 277/359 patients) was not significantly different between the two groups of patients [MRD <0·01% *TCF3-PBX1*: 16/23 (70%) vs. 169/277 (61%) respectively, $P = 0{\cdot}417$]. There were no significant differences according to good MRD response (MRD <0·01%) between patients with isolated t(1;19)/der(19)t(1;19) and those with t(1;19)/der(19)t(1;19) with ACA, as well as between patients with balanced rearrangements and der(19)t(1;19). Only two patients with *TCF3-PBX1* received an alloHSCT due to an end-consolidation MRD level of 0·05% and to poor response to the first induction cycle respectively. One of them is alive in third CR after chimeric antigen receptor T cells targeting CD19 (CART19) therapy and the second died due to a concomitant melanoma, with ALL in CR. The remaining patients with *TCF3-PBX1* completed delayed consolidation and maintenance (16 patients), relapsed during consolidation (five), died in consolidation (one), withdrew from the protocol (one) or were under consolidation (one).

The median follow-up of alive patients using the reverse Kaplan–Meier method was 3·59 years [95% confidence interval (CI) 2·10–5·80, range 0·20–7·25] for the patients

Table I. Comparison of the main characteristics of patients with *TCF3-PBX1* and patients with other B-cell precursor acute lymphoblastic leukaemia with evaluable cytogenetics.

	TCF3-PBX1 ($n = 26$)	Remaining B-cell precursor ALL ($n = 359$)	*P*
Age, years			
Median (range)	36 (17–60)	35 (15–60)	0·675
Gender, *n* (%)			
Male	7 (27)	197 (55)	0·006
Female	19 (73)	162 (45)	
ECOG PS score, *n/N* (%)			
0	5/22 (23)	109/339 (32)	0·623
1	14/22 (64)	177/339 (52)	
≥2	3/22 (14)	53/339 (16)	
WBC count, $\times 10^9$/l			
Median (range)	16·2 (0–199.5)	12 (0·2–638)	0·144
Mediastinal mass, *n/N* (%)			
No	22/22 (100)	339/346 (98)	1·000
Yes	0	7/346 (2)	
CNS involvement, *n/N* (%)			
No	21/24 (88)	311/336 (93)	0·417
Yes	3/24 (12)	25/336 (7)	
Phenotype, *n/N* (%)			
Pro-B	0	67 (19)	<0·001
Common B	9/24 (37)	231 (64)	
Pre-B	15/24 (63)	61 (17)	

ALL, acute lymphoblastic leukaemia; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *TCF3-PBX1*, transcription factor 3-pre-B-cell leukaemia homeobox 1; WBC, white blood cell.

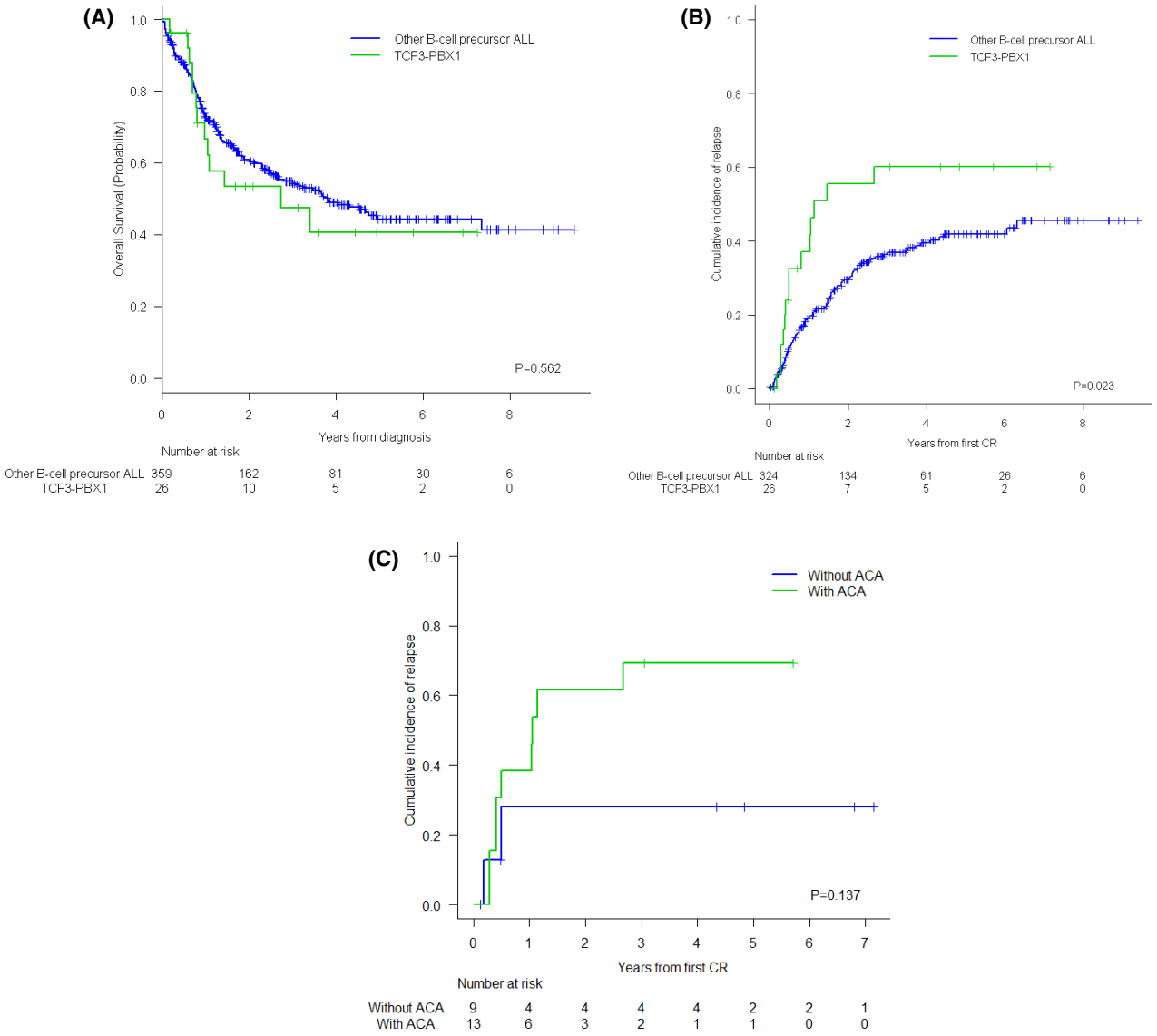

Fig 1. (A) Probability of overall survival for patients with transcription factor 3-pre-B-cell leukaemia homeobox 1 (*TCF3-PBX1*) rearrangement and the other B-cell precursor acute lymphoblastic leukaemia (ALL) patients with evaluable cytogenetics. (B) Cumulative incidence of relapse for patients with *TCF3-PBX1* rearrangement and the other B-cell precursor ALL patients with evaluable cytogenetics. (C) Cumulative incidence of relapse among patients with *TCF3-PBX1* rearrangement depending on the presence *versus* absence of additional cytogenetic alterations (ACA). [Colour figure can be viewed at wileyonlinelibrary.com]

with *TCF3-PBX1* and 3·71 (95% CI 3·27–4·20, range 0·13–9·47) for the other patients with BCP ALL. The probability of OS for patients with *TCF3-PBX1* was similar among the three protocols and was not significantly different from that of the remaining patients with BCP ALL [5-year OS 41% (95% CI 19–63%) vs. 44% (95% CI 38–50%), $P = 0·562$] (Fig 1A). The OS was better for patients with isolated t(1;19)/der(19)t(1;19) than for those with t(1;19)/der(19)t(1;19) with ACA [5-year OS 59% (95% CI 23–95%) vs. 31% (95% CI 0–62%), $P = 0·558$]. Patients aged <35 years had a significantly better OS than those ≥35 years [3-years OS 77% (95% CI 49–100%) vs. 25% (95% CI 1–49%), $P = 0·002$].

Patients with *TCF3-PBX1* had a significantly higher CIR than the remaining BCP ALL cases [5-year CIR of 60% (95% CI 36–77%) for *TCF3-PBX1* vs. 42% (95% CI 35–48%) respectively; $P = 0·023$) (Fig 1B). The higher relapse propensity seen in patients with *TCF3-PBX1* was mainly observed in those with ACA (5-year CIR 69% [33–89%] vs. 28% [3–63%], $P = 0·137$] (Fig 1C). In addition, younger patients had a trend for lower CIR than those aged ≥35 years [2-year CIR 40% (95% CI 11–69%) vs. 70% (95% CI 31–90%), $P = 0·073$]. Patients with both adverse prognostic factors (aged ≥35 years with ACA, nine patients) showed a trend for higher CIR compared with the remaining 13 patients [2-year CIR 67% (95% CI 20–90%] vs. 36% (95% CI 10–63%),

$P = 0{\cdot}089$]. All patients aged ≥35 years with ACA relapsed, which correlated with poorer OS for this subgroup [2-year OS 22% (95% CI 0–49%) vs. 74% (95% CI 48–100%), $P = 0{\cdot}020$]. The Fine–Gray model showed that age was the only predictor for CIR in patients with *TCF3-PBX1* (hazard ratio 4·433, 95% CI 1·014–19·380; $P = 0{\cdot}048$).

The outcome of the 14 relapsing patients was poor, despite six of them being rescued with blinatumomab (three) or inotuzumab (three), followed by CART19 in two of them. Currently, four patients are alive. The OS of the patients with *TCF3-PBX1* after first relapse was not different from that of the other patients with BCP ALL (data not shown).

Disease progression was the main cause of death among patients with *TCF3-PBX1* (10/13, 77%), while three of 13 patients (23%) died from NRM. In the remaining BCP ALL, death by disease progression was observed in 94/160 (59%) and 66/160 (41%) died from NRM (transplant-related mortality in 13 of them).

Discussion

The present analysis of adolescent and adult patients treated with MRD-oriented protocols shows that patients with *TCF3-PBX1* have a high probability of relapse, especially those aged >35 years with ACA, despite excellent response to treatment and scarce need of alloHSCT according to the MRD status. The relapse-associated mortality in these patients might counteract the higher NRM registered in the non-*TCF3-PBX1* group, explaining the similar OS of these groups.

Age was a prognostic factor for patients with *TCF3-PBX1*, as shown in any ALL subtype. The median age of the patients with *TCF3-PBX1* in our present series (36 years) was older than that of other similar studies[2,3,5] and the frequency of alloHSCT was lower,[4] as alloHSCT indication was exclusively based on MRD-status after induction and consolidation.

The presence of ACA showed a trend for higher relapse, as has also been shown in patients with Ph^+-ALL treated within PETHEMA trials.[12] Unfortunately, detailed genomic data are not available, although the ACA could indicate the presence of recurrent abnormalities with potential poor outcome (i.e. *MYB*, *CDKN2A/B* and *RB1*).[13,14] Besides MRD, genetic differences at the molecular level might contribute, at least in part, to the different outcomes observed among patients with *TCF3-PBX1*.

In addition to the lack of genomic data, the main limitation of the present study, and others showing similar frequency, is the low number of patients, despite including FISH analysis to ensure full detection of patients with *TCF3-PBX1* when available. Given the low incidence of this ALL subtype and the conflicting data in the literature, a pooling of data from several studies or a meta-analysis might help to give more reliable results. From our present results, patients with *TCF3-PBX1* aged >35 years with ACA might benefit from consolidation with immunotherapy followed or not by alloHSCT. In addition, targeted therapies with kinase inhibitors and/or phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) inhibitors may also be of special interest for this subset of patients.[15]

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Conflicts of interest

The authors have no competing interests.

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