Outcome of 421 adult patients with Philadelphia-negative acute lymphoblastic leukemia treated under an intensive program inspired by the GIMEMA LAL1913 clinical trial: a Campus ALL study

Davide Lazzarotto,[1] Marco Cerrano,[2] Cristina Papayannidis,[3] Sabina Chiaretti,[4] Federico Mosna,[5] Nicola Fracchiolla,[6] Patrizia Zappasodi,[7] Silvia Imbergamo,[8] Maria Ilaria Del Principe,[9] Monia Lunghi,[10] Federico Lussana,[11] Matteo Piccini,[12] Monica Fumagalli,[13] Michelina Dargenio,[14] Prassede Salutari,[15] Fabio Forghieri,[16] Teresa Giulia Da Molin,[17,18] Massimiliano Bonifacio,[17,18] Matteo Olivi,[19] Fabio Giglio,[20] Silvia Trappolini,[21] Matteo Leoncin,[22] Antonino Mulè,[23] Mario Delia,[24] Crescenza Pasciolla,[25] Francesco Grimaldi,[26] Benedetta Cambò,[27] Lidia Santoro,[28] Fabio Guolo,[29,30] Paola Minetto,[29,30] Marzia Defina,[31] Patrizia Chiusolo,[32,33] Matteo Fanin,[1,34] Endri Mauro,[35] Lara Aprile,[36] Carla Mazzone,[37] Fabio Trastulli,[38] Maria Ciccone,[39] Marco De Gobbi,[40] Alessandro Cignetti,[41] Eleonora De Bellis,[42] Valentina Mancini,[43] Alfonso Piciocchi,[44] Marco Vignetti,[44] Giovanni Marsili,[44] Irene Della Starza,[4,44] Renato Fanin,[1,34] Mario Luppi,[16] Felicetto Ferrara,[38] Giovanni Pizzolo,[17,18] Renato Bassan,[22] Robin Foà[4] and Anna Candoni[1,16]

[1]Clinica Ematologica - Centro Trapianti e Terapie Cellulari, Azienda Sanitaria Universitaria Friuli Centrale, Udine; [2]S.C. Ematologia, AOU Città della Salute e della Scienza - Presidio Molinette, Torino; [3]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna; [4]Ematologia, Dipartimento di Medicina Traslazionale e di Precisione, "Sapienza" Università di Roma, Roma; [5]Ematologia e Centro Trapianti di Midollo Osseo, Azienda Sanitaria dell'Alto Adige, Bolzano; [6]U.O. Ematologia, IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano; [7]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia; [8]Dipartimento Strutturale Aziendale Medicina, University of Padova, Padova; [9]Department of Biomedicine and Prevention, University of Rome Tor Vergata, Roma; [10]Division of Hematology, Department of Translational Medicine, AOU Maggiore della Carità, Università del Piemonte Orientale, Novara; [11]Hematology and Bone Marrow Transplantation Unit, Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo; [12]SODc Ematologia, Azienda Ospedaliera Universitaria Careggi, Firenze; [13]Ematologia, Ospedale San Gerardo, ATS Brianza, Monza; [14]S.C. Ematologia, Ospedale Vito Fazzi, Lecce; [15]Hematology Unit, Ospedale Civile Santo Spirito, Pescara; [16]Clinica Ematologica, Azienda Ospedaliero Universitaria di Modena, Dipartimento Scienze Mediche e Chirurgiche, UNIMORE, Modena; [17]Department of Engineering for Innovation Medicine, Section of Hematology, University of Verona, Verona; [18]Department of Medicine, Azienda Ospedaliera Universitaria Integrata di Verona, Verona; [19]Department of Oncology and Hematology, A.O.U. Città della Salute e della Scienza di Torino, Torino; [20]Unità di Ematologia e Trapianto di Midollo Osseo, IRCCS Ospedale San Raffaele di Milano, Milano; [21]S.O.D. Clinica Ematologica, Azienda Ospedaliero-Universitaria Ospedali Riuniti Umberto I, Ancona; [22]UOC Ematologia, Azienda Ulss3 Serenissima, Ospedale dell'Angelo, Mestre; [23]Divisione di Ematologia ad Indirizzo Oncologico, A.O. Ospedali Riuniti Villa Sofia-Cervello, Palermo; [24]UO Ematologia con Trapianto - Azienda Ospedaliero-Universitaria-Consorziale Policlinico di Bari, Bari; [25]U.O. di Ematologia, IRCCS Istituto Tumori Giovanni Paolo II, Bari; [26]Dipartimento di Medicina Clinica e Chirurgia, AOU Federico II, Napoli; [27]Hematology and BMT Unit, Department of Clinical and Experimental Medicine, University of Parma, Parma; [28]U.O.C. Ematologia e Trapianto di Midollo Osseo, Azienda Ospedaliera di Rilievo Nazionale e di Alta Specialità "San Giuseppe Moscati", Avellino; [29]Clinica Ematologica, Dipartimento di Medicina Interna (DiMI), Università degli Studi di Genova, Genova; [30]IRCCS Ospedale Policlinico San Martino, Genova; [31]UOC Ematologia, Azienda Ospedaliero Universitaria Senese, Siena; [32]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma; [33]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del

Correspondence: D. Lazzarotto
davide.lazzarotto@asufc.sanita.fvg.it

A. Candoni
acandoni@unimore.it

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Sacro Cuore, Roma; [34]Dipartimento di Medicina, Università degli Studi di Udine, Udine; [35]Hematology Unit, Santa Maria di Ca' Foncello Hospital, Treviso; [36]S.C. Ematologia, Ospedale S.G. Moscati, Taranto; [37]Haematology, Department of Medicine, Ospedale St. Eugenio, Roma; [38]Hematology, Hospital "Antonio Cardarelli", Napoli; [39]UO Ematologia, Dipartimento di Medicine Specialistiche, Azienda Ospedaliero-Universitaria Arcispedale S. Anna, Ferrara; [40]Department of Clinical and Biological Sciences, San Luigi Gonzaga Hospital, University of Turin, Orbassano; [41]SCDU Ematologia e Terapie Cellulari, AO Ordine Mauriziano, Torino; [42]UCO Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste; [43]ASST Grande Ospedale Metropolitano Niguarda, Milano and [44]Centro Dati Fondazione GIMEMA Franco Mandelli, Roma, Italy

Abstract

The introduction of pediatric-inspired regimens in adult Philadelphia-negative acute lymphoblastic leukemia (Ph$^-$ ALL) has significantly improved patients' prognosis. Within the Campus ALL network, we analyzed the outcome of adult Ph$^-$ ALL patients treated according to the GIMEMA LAL1913 protocol outside the clinical trial to compare the real-life data with the study results. We included 421 consecutive patients; median age 42 years. The complete remission (CR) rate after the first course of chemotherapy was 94%, and measurable residual disease (MRD) negativity after the third course was achieved in 72% of patients. The 3-year overall survival (OS) and disease-free survival (DFS) were 67% and 57%, respectively. In a multivariate analysis, MRD positivity negatively influenced DFS. In a time-dependent analysis including only very high-risk (VHR) and MRD positive cases, transplanted (hematopoietic stem cell transplantation [HSCT]) patients had a significantly better DFS than non-HSCT patients (P=0.0017). During induction, grade ≥2 pegaspargase-related hepato-toxicity was observed in 25% of patients (*vs*. 12% in the GIMEMA LAL1913 trial, P=0.0003). In this large, real-life cohort of Ph$^-$ ALL, we confirmed the very high CR rate and a superimposable OS and DFS compared to the GIMEMA LAL1913 clinical trial (CR rate after C1, 94% *vs*. 85%, P=0.0004; 3-year OS, 67% *vs*. 67%, P=0.94; 3-year DFS, 57% *vs*. 63%, P=0.17). HSCT confirms its important role in VHR and MRD-positive patients. The rate of pegaspargase-related toxicity was significantly higher in the real-life setting, emphasizing the importance of dose adjustment in the presence of risk factors to avoid excessive toxicity.

Introduction

There is still no definitive consensus on the optimal treatment regimen for adult Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph$^-$ ALL) to optimally balance efficacy and toxicity, as shown by the different treatment backbones employed by cooperative study groups.[1-7] Nonetheless, over recent years, numerous phase II and phase III clinical trials from different countries have been associated with better results compared to those from previous experiences.[1-7] These improvements have been achieved using intensive pediatric-inspired protocols, new formulations of asparaginase, and revised stratification models which included measurable residual disease (MRD) monitoring, in addition to baseline risk factors.[8-10] However, data on the real-life applicability of therapeutic regimens tested in clinical trials, which inherently enroll selected patient populations, are very limited.

Recently, the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) published the results of the LAL1913 clinical trial, which included 203 homogeneously treated adult Ph$^-$ ALL patients with a pediatric-inspired protocol.[1] After the completion of this study, most Italian hematology centers used the same therapeutic program in their clinical practice while the new protocol for Ph$^-$ ALL was under discussion. In this paper, we report the efficacy and safety data of a chemotherapy program performed according to the GIMEMA LAL1913 protocol in adult patients with Ph$^-$ ALL treated outside the clinical trial, in a real-life setting.

Methods

Patients and objectives of the study

We included 421 consecutive adult patients with newly diagnosed Ph$^-$ ALL or lymphoblastic lymphoma (LL, with <20% bone marrow blasts) treated according to the GIMEMA LAL1913 protocol,[1] outside the clinical trial, between September 2016 and December 2022. The data were collected from 39 hematology centers that are part of the Campus ALL network in Italy.

The main objectives of the study were to compare the complete remission (CR) rate, the overall survival (OS), and the disease-free survival (DFS) between the real-life cohort (421 cases) and the GIMEMA LAL1913 clinical trial population (203 cases). Secondary endpoints included evaluation of the treatment toxicity and the allogeneic stem cell transplantation (HSCT) rate according to the risk-group at diagnosis. Diagnostic procedures such as immunophenotyping, cytogenetics and molecular studies were carried out according to the GIMEMA LAL1913 protocol indications.[1,2] The Philadelphia-like signature was not routinely tested in this real-life population. In line with the GIMEMA LAL1913 trial, 3 risk classes were defined at diagnosis (as reported in the *Online Supplementary Appendix*).

This observational study was approved by the Ethics Committee of Friuli Venezia Giulia, Italy (ethical approval number CEUR-2022-Os-03) and conducted in accordance with the Declaration of Helsinki (revised 2008).

Treatment protocol

All patients were treated according to the GIMEMA LAL1913 protocol as described by Bassan *et al*. and detailed in *Online Supplementary Table S1*.[1] Antibiotic, antimycotic and antiviral prophylaxis, and pegaspargase toxicity management were administered according to the policy of each center. Treatment-related toxicity was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Measurable residual disease analysis

Measurable residual disease analysis was carried out on bone marrow samples through real-time quantitative polymerase chain reaction (RTq-PCR) for immunoglobulin (IG) or T-cell receptor (TR) gene rearrangements following the EuroMRD guidelines[11] in 3 reference laboratories (as in the GIMEMA LAL1913 trial) or locally through multiparameter flow cytometry (MFC) targeting leukemia-associated immunophenotype in patients lacking suitable molecular probes. Similarly to the GIMEMA LAL1913 trial, data on MRD were collected at 4 specific timepoints: end of induction week 4 (TP1), week 10 (end of course 3, TP2), week 16 (end of course 5, TP3), and week 22 (end of course 7, TP4). Patients with low positive ($<10^{-4}$) or negative TP2-3 and negative TP4 (or negative TP2-3 when TP4 was missing) were defined as MRD-negative (MRD-neg), while those with TP2-3 $\geq 10^{-4}$ and/or positive TP4 were defined as MRD-positive (MRD-pos), according to the LAL1913 clinical trial.

Statistical analysis

The comparison between baseline characteristics among subgroups was obtained using Fisher's exact or χ^2 test for categorical variables, Student *t* test for normally distributed variables, and Mann-Whitney test for non-normally distributed variables. Logistic regression was used to study variables influencing the achievement of MRD-negativity at TP2. Median follow-up time was calculated among survivors and was last updated in June 2023.

The response evaluation criteria are reported in the *Online Supplementary Appendix*. OS was calculated from the date of diagnosis to the date of the last follow-up or to the date of death from any cause. DFS was calculated from the date of achieving first CR to the date of the last follow-up, relapse or death from any cause. DFS stratification for MRD followed the definition for MRD-neg and MRD-pos described above using the available timepoints for each patient. OS and DFS were estimated according to the Kaplan-Meier method and the differences between groups were compared with the log-rank test. Univariate and multivariate analyses were carried out by Cox regression for OS and DFS.

Simon-Makuch plot was used to assess the time-dependent effects of HSCT and Mantel-Byar test was used for comparison of survival curves.

The same descriptive statistics were used to compare the characteristics of the real-life and the LAL1913 clinical trial populations. To compare OS and DFS, a subclass matching propensity score was performed (5 quantile classes) considering the following variables: age, sex, risk, lineage, and transplant. All 602 observations were matched, and the real-life data were weighted according to subclassification. Propensity score estimates were calculated using a logistic regression model. A summary of the characteristics of the patients in the propensity score matching is reported in *Online Supplementary Table S2*.

$P<0.05$ was considered statistically significant.

Results

Patients' characteristics

The main characteristics of the 421 patients are summarized in Table 1. Median age was 42 years (range 18-80) and was significantly lower in T-ALL/LL patients (38.5 *vs*. 45, $P=0.0009$); 23% (N=97) were older than 55 years, 52.5% (N=221) had B-ALL, and 12% (N=50) had LL (of which N=45 were T-lineage, $P<0.0001$).

The median white blood cell (WBC) count was significantly higher in T-ALL ($P<0.0001$), as was also the involvement of lymph nodes and mediastinum (42% and 47% of patients, respectively). Central nervous system (CNS) involvement was documented in 9% (N=37) of patients at disease onset (more frequently in T-ALL/LL: 12.5% *vs*. 5%, $P=0.0149$).

As for cytogenetics / genetics (evaluable in 81% of patients, N=342), 15 patients had a *KMT2A*;11q23 rearrangement, 45 had other adverse karyotypes, while a t(1;19)/*TCF3::PBX1* translocation was detected in 5 patients and a hyperdiploidy in 15. The Philadelphia-like signature was not routinely tested (see Methods).

Overall, 49% of patients were standard risk (SR), 10% high risk (HR), and 41% very high risk (VHR). T-ALL/LL patients more frequently displayed VHR features (52% *vs*. 30% of B-ALL/LL, $P<0.0001$).

The median follow-up of the entire population was 24.6 months. At the last follow-up, 306 patients (73%) were alive (251/306 [82%] in CR1) and 115 (27%) had died (64/115 [56%] due to underlying disease; 24/115 [21%] due to transplant-related mortality; 9/115 [8%] deaths during induction; 5/115 [4%] deaths in CR during subsequent courses of chemotherapy; 13/115 [11%] due to other causes).

Treatment and response

All 421 patients received the first course of therapy (C1) and 358 (85%) of them were able to continue the treatment up to the third course (C3). Prior to C3 we recorded 15 deaths,

Table 1. Characteristics of the 421 study patients.

Characteristics	All patients N=421	B-ALL/LL N=221	T-ALL/LL N=200
Age in years, median (range) ≤40, N (%) 41-55, N (%) >55, N (%)	42.0 (18-80) 199 (47) 125 (30) 97 (23)	45.0 (18-80) 87 (39) 66 (30) 68 (31)	38.5 (18-72) 112 (56) 59 (29.5) 29 (14.5)
Male, N (%)	248 (59)	111 (50)	137 (68.5)
Diagnosis, N (%) ALL LL	 371 (88) 50 (12)	 216 (98) 5 (2)	 155 (77.5) 45 (22.5)
ECOG PS, N 0;1;2;3;4;NA	 212;147;42;15;3;2	 122;77;19;3;0;0	 90;70;23;12;3;2
Hemoglobin g/dL, median (range)	10.7 (4.1-17.2)	9.3 (4.1-15.1)	12.3 (4.2-17.2)
WBC x10^9/L, median (range) ≤30, N (%) 31-100, N (%) >100, N (%)	9.9 (0.2-626.9) 304 (72) 66 (16) 51 (12)	6.9 (0.2-626.9) 170 (77) 31 (14) 20 (9)	12.2 (0.5-538.0) 134 (67) 35 (17.5) 31 (15.5)
PB blasts %, median (range)	38.0 (0.0-100.0)	40.5 (0.0-100.0)	30.0 (0.0-100.0)
BM blasts %, median (range)	80.0 (0.0-100.0)	85.0 (0.0-100.0)	73.0 (0.0-100.0)
Platelets x10^9/L, median (range)	78 (4-753)	63.5 (8-400)	115 (4-753)
Hepatomegaly, N (%)	27 (6)	12 (5)	15 (7.5)
Splenomegaly, N (%)	44 (10.5)	18 (8)	26 (13)
Lymphadenopathy, N (%)	110 (26)	26 (12)	84 (42)
Mediastinal mass, N (%)	96 (23)	2 (1)	94 (47)
CNS involvement, N (%)	37 (9)	12 (5)	25 (12.5)
Other involved sites, N (%) testis/ovary:skin	5 1:4	- -	- -
Immunophenotype, N (%) B: pro, common, pre, MPAL, UND T: ETP, pro, pre, cortical, mature, MPAL, UND	 221 (52.5) 200 (47.5)	 39,130,23,5,24 -	 - 40,15,23,57,13,4,48
Cytogenetics/genetics, N (%) Evaluable Normal Adverse t(4;11)/*KMT2A::AFF4*, t(11;19) Other[a] Non-adverse t(1;19)/*E2A::PBX1* Hyperdiploid Other non-adverse	 342 (81.2) 174 (51) 60 (17) 15 45 108 (32) 5 15 88	 191 (86.4) 78 45 15 30 67 5 15 48	 151 (75.5) 96 15 - 15 40 - 0 40
Risk stratification, N (%) Evaluable Standard risk High risk Very high risk	 420/421 (99.8) 207 (49) 42 (10) 171 (41)	 221/221 (100) 120 (54) 34 (15) 67 (30)	 199/200 (99.5) 87 (44) 8 (4) 104 (52)

ALL: acute lymphoblastic leukemia; LL: lymphoblastic lymphoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status; NA: not available; WBC: white blood cells; PB: peripheral blood; BM: bone marrow; CNS: central nervous system; MPAL: mixed-phenotype acute leukemia; UND: undefined; ETP: early T precursor. [a]Other than t(4;11)/*KMT2A* rearrangement: 11q23, +8, -7, del6q, t(8;14) abnormalities, low hypodiploidy (30-39 chromosomes), near triploidy (60-78 chromosomes) or complex karyotype with ≥5 unrelated anomalies.

9 during induction (2%), 3 during consolidation (7 of which due to infection), and 3 unrelated to disease or therapy, while 40 patients switched to an alternative treatment, 26 (65%) due to refractoriness or early progression (14 after C1 and 12 after C2) and 14 (35%) due to adverse events (10 after C1 and 4 after C2). Eight patients had a short follow-up (too early for analysis) and had not undergone C3 at data cut off. Overall, only 6% of the entire patient population (26/421) was refractory after C2.

The morphologic CR rate after C1 was 94% (356/379) and after C2 95% (329/347) of evaluable patients; not evaluable patients were those with LL without marrow involvement and those in whom bone marrow was not studied. The early death rate was 3% (N=12) of the whole population.

After C3, 146 patients (35%) underwent a HSCT in first line; in 16% of patients (N=24), the procedure was preceded by immunotherapy for MRD persistence (N=22 blinatumomab, N=2 inotuzumab). The two main indications for HSCT were: VHR disease (70.5%, N=103) and MRD positivity (21%, N=31). HSCT was more frequently carried out in T-ALL patients (47% *vs*. 31%, *P*=0.002). Overall, 129 SR-MRD-neg patients were able to proceed to maintenance. Globally, 39 patients were treated with immunotherapy (N=35 blinatumomab, N=3 inotuzumab, N=1 daratumumab) for MRD persistence after first-line chemotherapy.

Measurable residual disease data were available in 381 patients (90.5%); 71% (N=269) were monitored by RTq-PCR for Ig/TR gene rearrangements, and the remaining 29% (N=112) by MFC. The rates of MRD negativity at TP1 and TP2 were, respectively, 46% and 67% of the evaluable patients (72% when excluding LL patients without MRD study on bone marrow).

A summary of the MRD response at the different timepoints is provided in Table 2; no difference was seen between B-ALL and T-ALL patients. A multivariate logistic regression analysis including age, risk category, lineage, ECOG score, and CNS involvement was carried out to study variables influencing the achievement of MRD negativity at TP2, and we found that the presence of a HR or a VHR risk class was the only factor associated with failure to achieve MRD negativity (Odds Ratio [OR] 0.38, Confidence Interval [CI]: 0.22-0.64, *P*=0.0003).

Side effects and toxicities

Chemotherapy dose reductions beyond those established by the LAL1913 protocol in patients aged >55 years were required during C1 in 118 patients (28%), due to either toxicity or infection in 50% of patients (N=59).

Table 3 summarizes pegaspargase-related toxicity. During C1, 382 patients (91%) received pegaspargase and 49% of them (189) developed a grade ≥2 related toxicity (mainly hepatic toxicity), while thrombosis, pancreatic toxicity and

Table 2. Summary of response according to different time points.

Response	All patients N=421	B-ALL N=216	T-ALL N=155	LL N=50
Response at TP1 in available cases, N (%)	379	209	147	23
MRD-pos/unk CR	181 (48)	108 (52)	66 (45)	7 (30)
MRD-neg CR	175 (46)	91 (43.5)	71 (48)	13 (57)
No CR	23 (6)	10 (5)	10 (7)	3 (13)
Response at TP2 in available cases, N (%)	344*	169	128	47*
MRD-pos CR	70 (20)	44 (26)	25 (19.5)	1 (2)
MRD-neg CR	231 (67)	115 (68)	96 (75)	20 (43)
MRD-unk CR	23 (7)*	4 (2)	2 (2)	17 (36)*
No CR	20 (6)*	6 (4)	5 (4)	9 (19)*
Response at TP3 in available cases, N (%)	168	89	64	15
MRD-pos CR	15 (9)	7 (8)	8 (12.5)	0
MRD-neg CR	144 (86)	77 (86.5)	52 (81)	15 (100)
MRD-unk CR	4 (2)	4 (4.5)	0	0
No CR	5 (3)	1 (1)	4 (6)	0
Response at TP4 in available cases, N (%)	141**	69	43	29**
MRD-pos CR	7 (5)	2 (3)	4 (9)	1 (3)
MRD-neg CR	112 (79)	61 (88)	39 (91)	12 (41)
MRD-unk CR	19 (13.5)**	5 (7)	0	14 (48)**
No CR	3 (2)**	1 (1.5)	0	2 (7)**

ALL: acute lymphoblastic leukemia; CR: complete remission; LL: lymphoblastic lymphoma; MRD: measurable residual disease; MRD-neg: MRD negative; MRD-pos: MRD positive; MRD-unk: MRD unknown; TP: timepoint. *Including 23 patients evaluated only with positron emission tomography (PET) scan (17 CR, 6 not CR) with bone marrow MRD not evaluable. **Including 16 patients evaluated only with PET scan (14 CR, 2 not CR) with bone marrow MRD not evaluable.

hypersensitivity reaction were rare (Table 3). The global rate of grade ≥2 pegaspargase-related toxicity at C2 was 32% (101/314). Pegaspargase was not administered at C2 in 12% of patients (47/382) due to previous related toxicity at C1. In addition, a drug dose reduction was required during C2 in 27% of patients receiving pegaspargase (86/314). During C5 and C6, the global rate of grade ≥2 pegaspargase-related toxicity was 38% and 30%, respectively. A pegaspargase dose reduction at C5 and C6 was required in 28% (50/177) and 35% (45/129) of cases, respectively. The drug was omitted at C5, due to the previous related toxicity, in 9% of patients and in 19% of patients at C6 (Table 3).

Pegaspargase-free courses (C3, C4, C7, and C8) were administered at the programmed full doses of chemotherapy in 93%, 93%, 89%, and 87% of patients, respectively.

Infectious complications were more frequently recorded during C1. Bacteremia/sepsis was the most common infection, observed in 14% of patients (N=59), followed by pneumonia in 11% (N=45); 20 cases of pneumonia (5% of the whole population) were mycotic. In addition, during C1, 22% (N=91) of patients developed febrile neutropenia. In the following courses, the number of patients developing bacteremia/sepsis was lower (between 1% and 9%); the courses with the highest number of events observed were C3, C6, and C7 (7%, 7%, and 9%, respectively). Also, the number of patients developing pneumonia was lower (between 0% and 4%) with similar percentages in the different courses. The number of patients developing febrile neutropenia beyond C1 ranged between 3% and 21% of patients, and again a higher number of events was observed at C3, C6, and C7 (17%, 18%, and 21%, respectively).

Survival analysis and prognostic factors

Three-year OS probability was 67% (median not reached), without any significant differences between patients aged ≤40 years and those aged 41-55 years (76% *vs*. 63%, *P*=0.28). However, both these groups had a significantly higher 3-year OS than patients aged >55 years (55%, Logrank test *P*=0.0007 *vs*. patients aged ≤40 years and *P*=0.041 *vs*. patients aged 41-55 years) (Figure 1A, C).

The 3-year DFS probability was 57% (median not reached), without any significant differences between patients aged ≤40 years and patients aged 41-55 years (61% *vs*. 60%, *P*=0.77). Again, both these groups had a significantly higher 3-year DFS than patients aged >55 years (46%, Logrank test *P*=0.011 *vs*. patients aged ≤40 and *P*=0.050 *vs*. patients aged 41-55) (Figure 1B, D).

Figure 2A shows the DFS curves for MRD-neg and MRD-pos patients. The 3-year DFS was 67% in MRD-neg *versus* 32% in MRD-pos patients (Logrank test, *P*<0.0001), respectively. In univariate analysis, a younger age predicted a better OS, while CNS involvement and MRD positivity predicted a worse OS. Younger age (≤55 years) also predicted a better DFS in univariate analysis, while MRD-pos, CNS involvement, high leukocyte count (>30x10^9/L), adverse cytogenetics, the presence of a *KMT2A* rearrangement, and the VHR risk class per se predicted a worse DFS. In multivariate analysis for OS and DFS, significance was retained only for MRD-pos (Figure 3).

To better analyze the effect of HSCT, a time-dependent analysis was performed for DFS. HSCT did not show any benefit when considering the whole population, but when we considered just VHR or MRD-pos patients, i.e., those who were transplant candidates according to the GIMEMA LAL1913 protocol, the impact of HSCT was significant (Mantel-Byar *P*=0.0017). The Simon-Makuch plot for DFS of VHR and/or MRD-pos patients according to HSCT is shown in Figure 2B.

Comparison with the results of the GIMEMA LAL 1913 trial

We compared the most important findings of this real-life observational study (including 421 cases) and the results of

Table 3. Summary of pegaspargase-related toxicity.

Study parameter	Course 1	Course 2	Course 5	Course 6
Patients, N	421	382	203	167
Received pegaspargase, N (%)	382/421 (91)	314/382 (82)	177/203 (87)	129/167 (77)
Pegaspargase not administered for previous pegaspargase toxicity, N (%)	NA	47/382 (12)	19/203 (9)	31/167 (19)
Pegaspargase dosing, N (%) Reduced Full dose	 61/382 (16) 321/382 (84)	 86/314 (27) 228/314 (73)	 50/177 (28) 127/177 (72)	 45/129 (35) 84/129 (65)
Pegaspargase-related toxicity G≥2, N (%) Hepatobiliary G≥2/≥3 Pancreatic G≥2/≥3 Thrombosis G≥2/≥3 Coagulopathy G≥2/≥3 Metabolic G≥2/≥3	189/382 (49) 96 (25) / 59 (15) 21 (6) / 11 (3) 7 (2) / 6 (2) 81 (21) / 24 (6) 13 (3) / 9 (2)	101/314 (32) 47 (15) / 15 (5) 1 (0.5) / 1 (0.5) 5 (2) / 4 (1) 57 (18) / 13 (4) 7 (2) / 4 (1)	67/177 (38) 36 (20) / 17 (10) 4 (2) / 3 (2) 0 / 0 37 (21) / 10 (6) 6 (3) / 4 (2)	39/129 (30) 19 (15) / 10 (8) 0 / 0 0 / 0 22 (17) / 6 (5) 2 (2) / 1 (1)

G: grade; NA: not applicable.

the GIMEMA LAL1913 clinical trial (including 203 cases) (Table 4).[1] The real-life population was slightly older, although the difference was not significant (median age, 42 *vs*. 40 years, *P*=0.5, with patients >55 years, 23% *vs*. 19%, *P*=0.33) and included a higher number of T-ALL/LL (47.5% *vs*. 31.5%, *P*=0.0002). Moreover, in the real-life population cohort, we observed a non-significantly higher proportion of HR+VHR patients (51% *vs*. 43%, *P*=0.09).

The CR rate at TP1 was higher in the real-life population (94% *vs*. 85%, *P*=0.0004), but the rate of MRD negativity at both TP1 and TP2 was lower (46% *vs*. 56%, *P*=0.04, and 72% *vs*. 80%, *P*=0.04, respectively).

Importantly, OS and DFS were similar in the 2 studies, with a 3-year OS of 67% *versus* 67%, *P*=0.94, and a 3-year DFS of 57% *versus* 63%, *P*=0.17, respectively (Figure 4). When weighed according to the propensity score used, 3-year OS and DFS were 67% and 55%, respectively (with *P*=0.94 and *P*=0.17, compared to the GIMEMA LAL1913 trial data). The rate of HSCT in first line was higher in the real-life setting (35% *vs*. 28%), though without reaching a significant difference (*P*=0.09).

Finally, we compared pegaspargase-related adverse events during C1, and we observed a higher rate of grade ≥2 hepatic toxicity in patients treated in the real-life setting compared to those included in the LAL1913 trial (25% *vs*. 12%, *P*=0.0003), while the rates of grade 3 pancreatic toxicity and the thrombotic events were similar in the 2 cohorts (3% *vs*. 1%, *P*=0.26, and 2% *vs*. 2%, *P*=1.00).

Discussion

Pediatric-inspired protocols have improved the outcome of Ph$^-$ ALL in adults,[8] as demonstrated by several trials yielding comparable results, with CR rates around 90%,

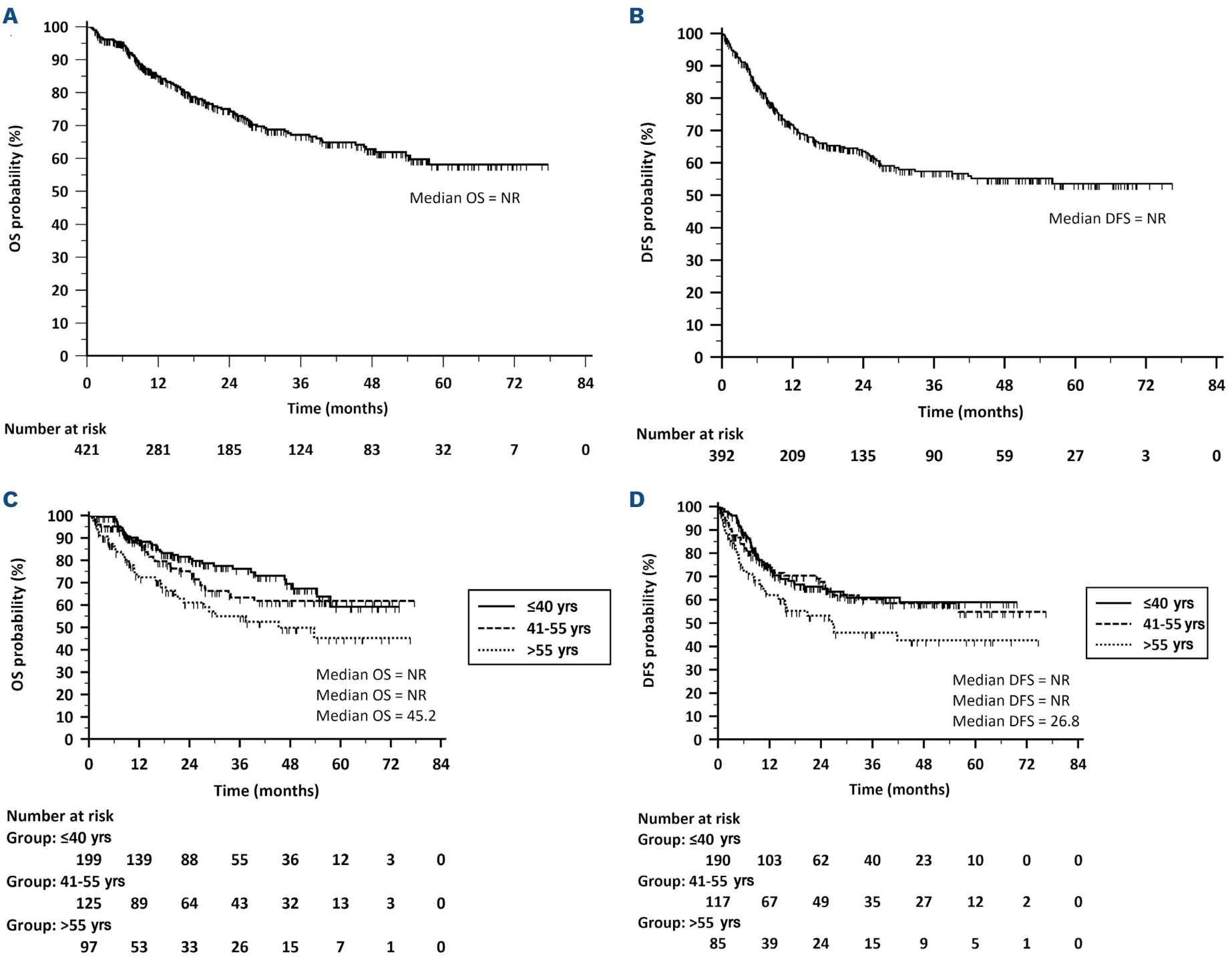


Figure 1. Overall survival and disease-free survival. (A and B) Overall survival (OS) and disease-free survival (DFS) of the entire study population. (C and D) Overall survival (OS) and disease-free survival (DFS) stratified for age (≤40, 41-55, >55 years). NR: not reached; yrs: years.

and OS and DFS rates above 60% at 3-5 years, despite the differences in trial design, and asparaginase formulations and dosage.[1-7] In trials including older adults (>55 years), this patient population presents worse results, with inferior CR rates and survival.[1-4] This is likely due to the problems in delivering optimal chemotherapy doses, increased rates of complications, and a different disease biology compared to younger patients.[3,4,12]

Despite the significant number of clinical trials using pediatric-inspired protocols in adult Ph$^-$ ALL, very limited data are available on the feasibility, toxicities and outcome of these protocols in the context of daily clinical practice outside of clinical trials.[13-16] Since the completion of the GIMEMA LAL1913 trial, the results of which have been recently published,[1] most Italian hematology centers have adopted this pediatric-inspired therapeutic program as the standard of care for the clinical management of newly diagnosed adult Ph$^-$ ALL. The current study conducted within the Campus ALL network and involving 39 hematology centers in Italy was thus aimed at analyzing the feasibility and performance of the LAL1913 program in the real-life context in terms of tolerability and outcome, and to compare these results with those obtained in the original clinical trial.[1] To our knowledge, this multicenter real-life study that included 421 adult Ph-ALL patients homogeneously treated according to a pediatric-inspired protocol (GIMEMA LAL1913)[1] is the largest available so far.

Some differences emerged between the characteristics of the real-life population compared to that of the clinical trial. The real-life cohort included more T-ALL (47.5% *vs.* 31.5%) and a

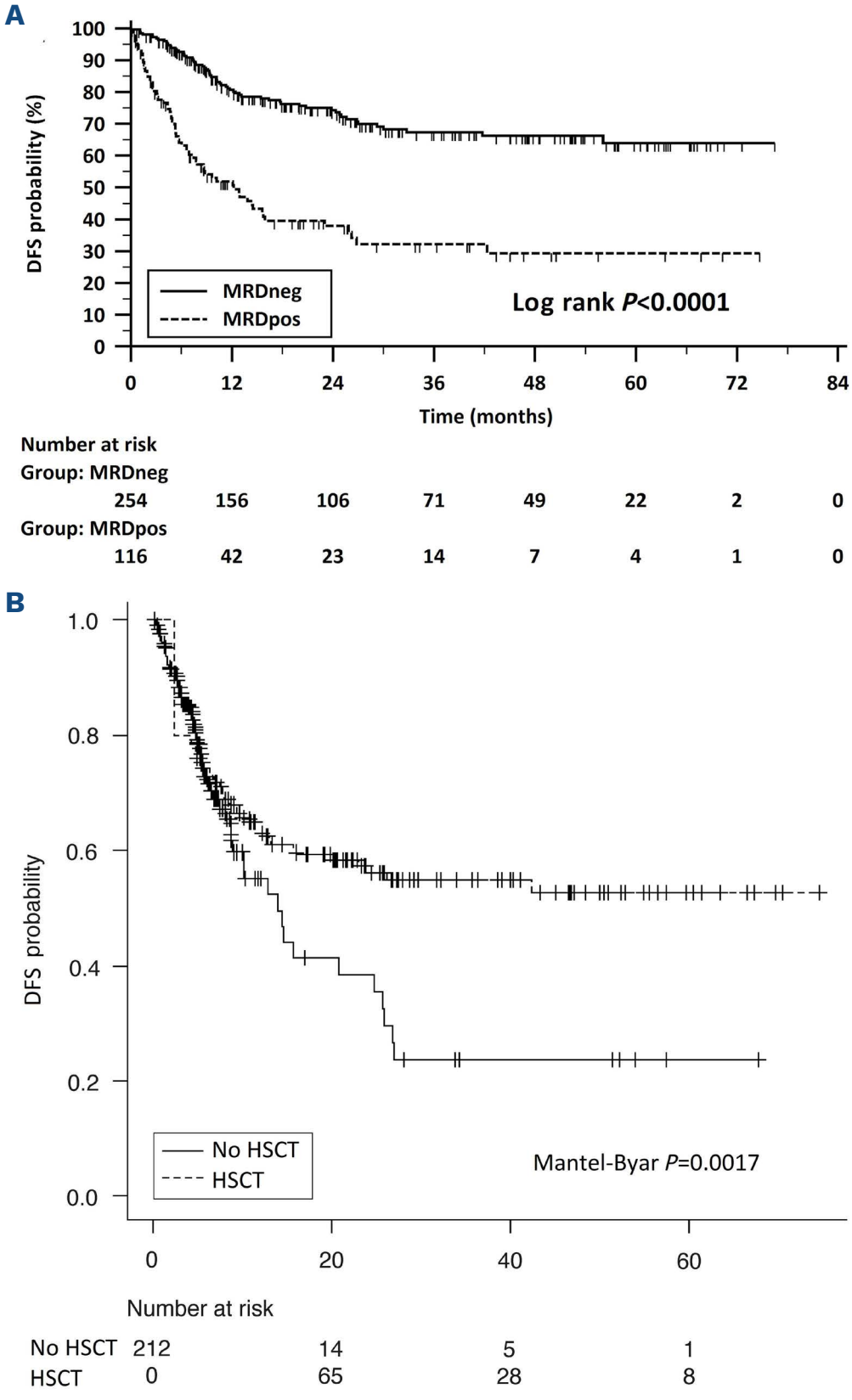
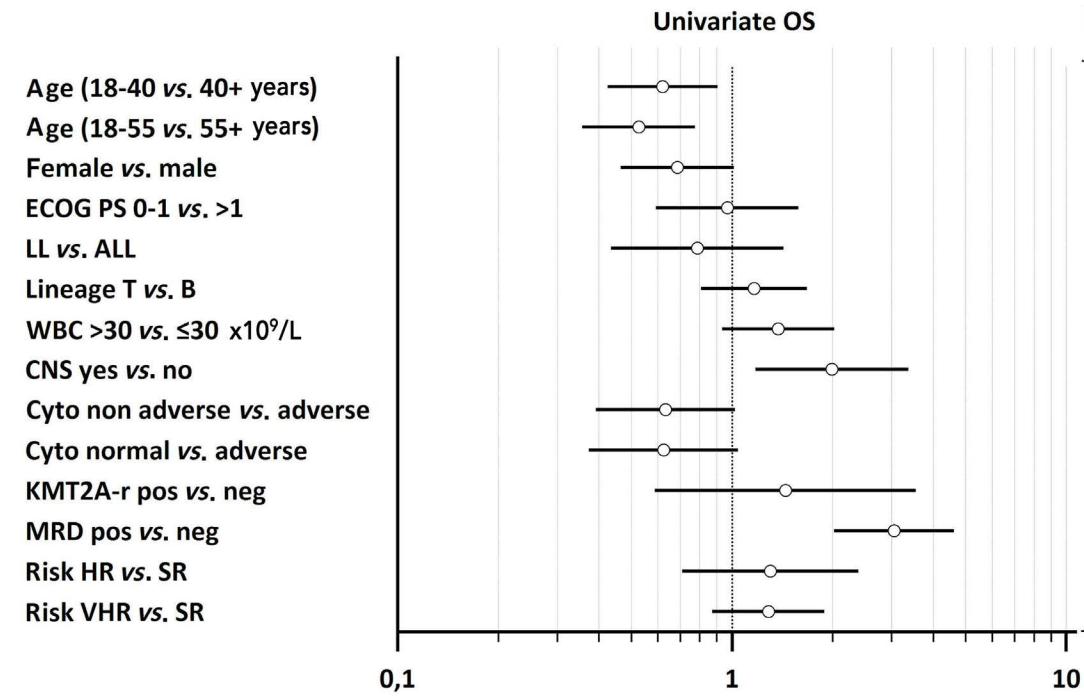


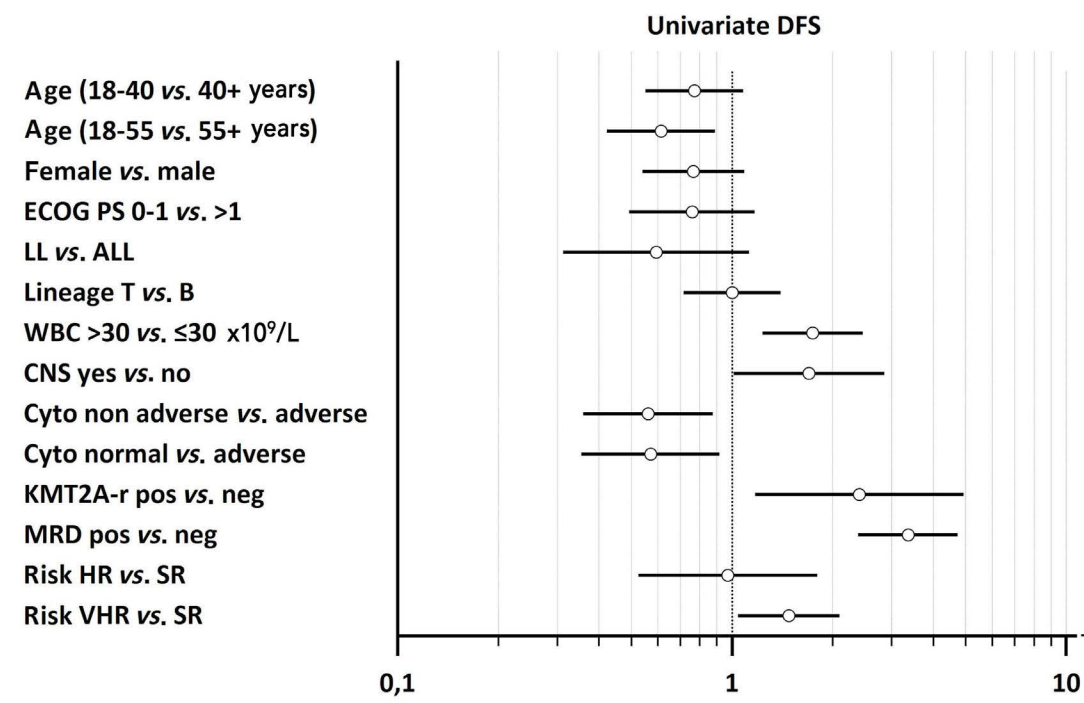
Figure 2. Disease-free survival according to measurable residual disease and allogeneic stem cell transplant. (A) Disease-free survival (DFS) stratified for measurable residual disease (MRD) status. (B) Simon-Makuch plot of DFS of very high-risk (VHR) and/or MRD-positive (MRDpos) patients according to allogeneic stem cell transplant (HSCT).

A



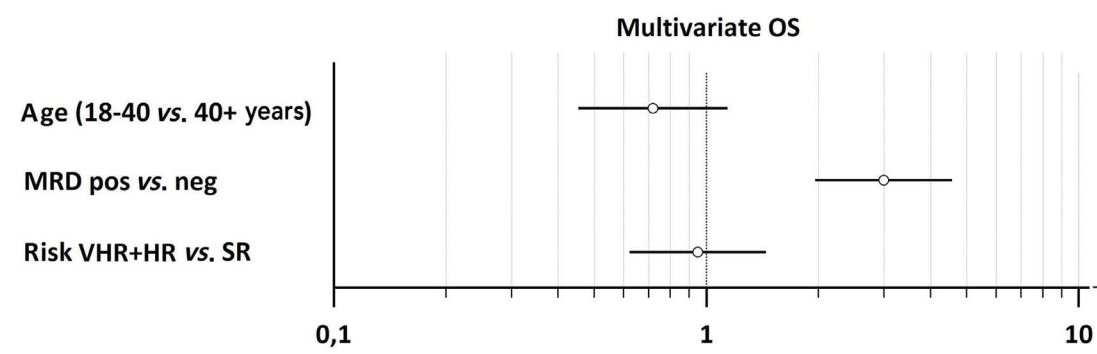
	Hazard Ratio	CI	*P*
Age (18-40 *vs.* 40+ years)	**0.6205**	**0.4251-0.9056**	**0.0138**
Age (18-55 *vs.* 55+ years)	**0.5260**	**0.3563-0.7766**	**0.0013**
Female *vs.* male	0.6863	0.4649-1.0131	0.0594
ECOG PS 0-1 *vs.* >1	0.9677	0.5926-1.5804	0.8963
LL *vs.* ALL	0.7878	0.4345-1.4283	0.4343
Lineage T *vs.* B	1.1647	0.8091-1.6766	0.4145
WBC >30 *vs.* ≤30 x10⁹/L	1.3746	0.9336-2.0238	0.1087
CNS yes *vs.* no	**1.9909**	**1.1758-3.3711**	**0.0108**
Cyto non adverse *vs.* adverse	0.6329	0.3917-1.0228	0.0631
Cyto normal *vs.* adverse	0.6243	0.3733-1.0441	0.0740
KMT2A-r pos *vs.* neg	1.4445	0.5878-3.5500	0.4251
MRD pos *vs.* neg	**3.0551**	**2.0210-4.6182**	**<0.0001**
Risk HR *vs.* SR	1.3019	0.7100-2.3871	0.3962
Risk VHR *vs.* SR	1.2843	0.8728-1.8898	0.2065

B



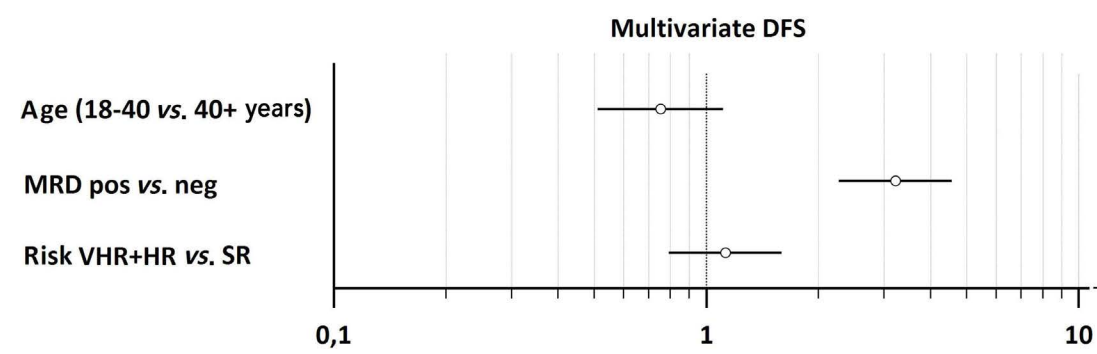
	Hazard Ratio	CI	*P*
Age (18-40 *vs.* 40+ years)	0.7724	0.5515-1.0819	0.1315
Age (18-55 *vs.* 55+ years)	**0.6133**	**0.4226-0.8899**	**0.0104**
Female *vs.* male	0.7662	0.5394-1.0884	0.1390
ECOG PS 0-1 *vs.* >1	0.7593	0.4391-1.1690	0.2134
LL *vs.* ALL	0.5939	0.3129-1.1270	0.1127
Lineage T *vs.* B	1.0009	0.7169-1.3975	0.9958
WBC >30 *vs.* ≤30 x10⁹/L	**1.7432**	**1.2329-2.4646**	**0.0018**
CNS yes *vs.* no	**1.7000**	**1.0107-2.8596**	**0.0466**
Cyto non adverse *vs.* adverse	**0.5610**	**0.3589-0.8769**	**0.0116**
Cyto normal *vs.* adverse	**0.5709**	**0.3549-0.9183**	**0.0215**
KMT2A-r pos *vs.* neg	**2.4052**	**1.1722-4.9353**	**0.0173**
MRD pos *vs.* neg	**3.3633**	**2.3864-4.7000**	**<0.0001**
Risk HR *vs.* SR	0.9703	0.5252-1.8001	0.9292
Risk VHR *vs.* SR	**1.4804**	**1.0442-2.0988**	**0.0284**

C



	Hazard Ratio	CI	*P*
Age (18-40 *vs.* 40+ years)	0.7190	0.4528-1.1417	0.1641
MRD pos *vs.* neg	**2.9925**	**1.9599-4.5693**	**<0.0001**
Risk VHR+HR *vs.* SR	0.9486	0.6222-1.4461	0.8071

D



	Hazard Ratio	CI	*P*
Age (18-40 *vs.* 40+ years)	0.7531	0.5108-1.1103	0.1543
MRD pos *vs.* neg	**3.2157**	**2.2671-4.5612**	**<0.0001**
Risk VHR+HR *vs.* SR	1.1246	0.7931-1.5948	0.5119

Figure 3. Univariate and multivariate analysis. (A) Univariate analysis for overall survival (OS). (B) Univariate analysis for disease-free survival (DFS). (C) Multivariate analysis for OS. (D) Multivariate analysis for DFS. ALL: acute lymphoblastic leukemia; CI: Confidence Interval; CNS: central nervous system; Cyto: cytogenetics; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HR: high risk; LL: lymphoblastic lymphoma; MRD: measurable residual disease; SR: standard risk; VHR: very high risk; WBC: white blood cell.

higher proportion of HR+VHR patients, albeit the difference was not significant (51% *vs*. 43%). Median age and the proportion of patients aged >55 years were comparable in the 2 cohorts (23% in real-life *vs*. 19% in clinical trial, *P*=0.33).

A high CR rate after C1 (94%) was observed in the real-life setting; this was even higher than the rate reported in the GIMEMA LAL1913 clinical trial (85%, *P*=0.0004). However, the rate of MRD-neg patients at both TP1 and TP2 was lower in the real-life cohort compared to the clinical trial results (46% *vs*. 56%, *P*=0.04, and 72% *vs*. 80%, *P*=0.04, respectively), and this can be explained by the higher number of HR and VHR patients included in our study, considering that this was the only variable that significantly influenced the achievement of MRD negativity at TP2. Interestingly, the OS and DFS observed in our real-life population were comparable to the results reported in the GIMEMA LAL1913 clinical trial (3-year OS, 67% *vs*. 67%, *P*=0.94; 3-year DFS, 57% *vs*. 63%, *P*=0.17). The CR and MRD-neg rates, OS and DFS were also in line with other published prospective clinical trials.[3,4,6]

Similar to other studies, age had an impact on OS in this real-life analysis,[1-4,14-16] but unlike the GIMEMA LAL1913 clinical trial, patients aged 41-55 years presented similar OS to patients aged ≤40 years, and only patients aged >55 years showed a significantly reduced survival.[1]

Furthermore, this study confirmed that biological features of the disease at diagnosis (cytogenetics, leukocytosis, *KMT2A* rearrangements) played an important role in DFS in univariate analysis, contributing to the definition of HR and VHR classes. This effect was not evident in the GIMEMA LAL1913 clinical trial, in which only patients with *KMT2A* rearranged ALL showed a significantly worse outcome.[1]

Table 4. Comparison between the study results and the GIMEMA LAL1913 clinical trial.

	Campus ALL study N=421	**GIMEMA LAL1913 trial N=203**	***P***
Age in years, median (range) ≤40, N (%) 41-55, N (%) >55, N (%)	42.0 (18-80) 199 (47) 125 (30) 97 (23)	39.8 (18-65) 103 (51) 61 (30) 39 (19)	0.5000 0.4773 0.9867 0.3300
Diagnosis, N (%) ALL LL B-ALL/T-ALL	 371 (88) 50 (12) 221/200	 183 (90) 20 (10) 139/64	 0.5702 0.5200 0.0002
WBC x10^9/L, median (range) ≤30, N (%) 31-100, N (%) >100, N (%)	9.9 (0.2-626.9) 304 (72) 66 (16) 51 (12)	7.1 (1.5-347.3) 159 (78) 31 (15) 13 (6)	0.1251 0.9910 0.0395
CNS involvement, N (%)	37 (9)	19 (9)	0.9559
Risk stratification, N (%) Standard risk (SR) High risk (HR) Very high risk (VHR)	 207 (49) 42 (10) 171 (41)	 115 (58) 20 (10) 68 (33)	 0.0994 0.9175 0.0951
CR at TP1, %	94	85	0.0004
MRD negativity at TP2 in available cases, %	72	80	0.0401
Refractory patients before C3, %	6	3	0.2030
First-line HSCT rate, %	35	28	0.0921
Median follow-up in months	25	39	-
3-year OS, % 3-year DFS, %	67 57	67 63	0.9400 0.1700
Pegaspargase toxicity, % Grade ≥2 hepatic toxicity at C1 Grade ≥3 pancreatic toxicity at C1 Grade ≥3 thrombosis at C1	 25 3 2	 12 1 2	 0.0003 0.2592 0.9988

ALL: acute lymphoblastic leukemia; C: course; CNS: central nervous system; CR: complete remission; DFS: disease-free survival; HSCT: allogeneic stem cell transplantation; LL: lymphoblastic lymphoma; MRD: measurable residual disease; OS: overall survival; TP: timepoint; WBC: white blood cells.

We also confirmed the crucial role of MRD monitoring in clinical practice and its important prognostic impact on OS and DFS, as observed in many clinical trials.[1,2,14,17-19]

Our real-life data also highlighted the prognostic impact of first-line HSCT in patients with unfavorable risk factors (VHR and/or MRD-pos), with results comparable to those reported in the GIMEMA LAL1913 clinical study. In our population, a proportion of patients was bridged to HSCT procedure with immunotherapy for MRD positivity. This option was not available in the GIMEMA LAL1913 trial. However, given that this approach is becoming standard clinical practice, and that several trials (such as the ongoing GIMEMA LAL2317) are exploring a sequential chemo-immunotherapy approach, the role of HSCT may change in the near future.[17,20,21]

In terms of tolerability, the highest rate of pegaspargase-related toxicity in our study was observed at C1, with 49% of patients experiencing at least one grade ≥2 adverse event. In particular, during C1, 25% of patients in this study developed grade ≥2 hepatic toxicity compared to 12% of patients in the GIMEMA LAL1913 clinical trial (*P*=0.0003). Overall, the pegaspargase-related toxicity observed compares favorably to other international reports in the literature.[22,23] This finding may reflect less attention to risk factors for pegaspargase-related toxicity (such as obesity, hepatopathies) and/or a less stringent patient selection in the real-life setting than in the GIMEMA LAL1913 clinical trial.

Infectious complications are a significant concern during the management of Ph$^-$ ALL patients.[24] In our analysis, infectious complications mainly occurred at C1, with 14% of patients developing bacteremia/sepsis and 11% of patients developing pneumonia (mycotic in nearly half of the cases). While pneumonia is not a common event in subsequent courses, the number of patients who developed bacteremia/sepsis reached 9% of cases, in line with previous studies involving Ph$^-$ ALL patients treated with intensive protocols.[6,7,13] Despite the low rate of early mortality observed in our study (3%, 12/421), infections were the main cause of death, affecting more than half of cases. This suggests the need to improve infection surveillance, prophylactic measures, and antimicrobial therapy.

In summary, our study demonstrates the feasibility and favorable outcome of a pediatric-inspired therapeutic regimen in a large real-world setting with CR rates and OS and DFS similar to those reported in the reference GIMEMA

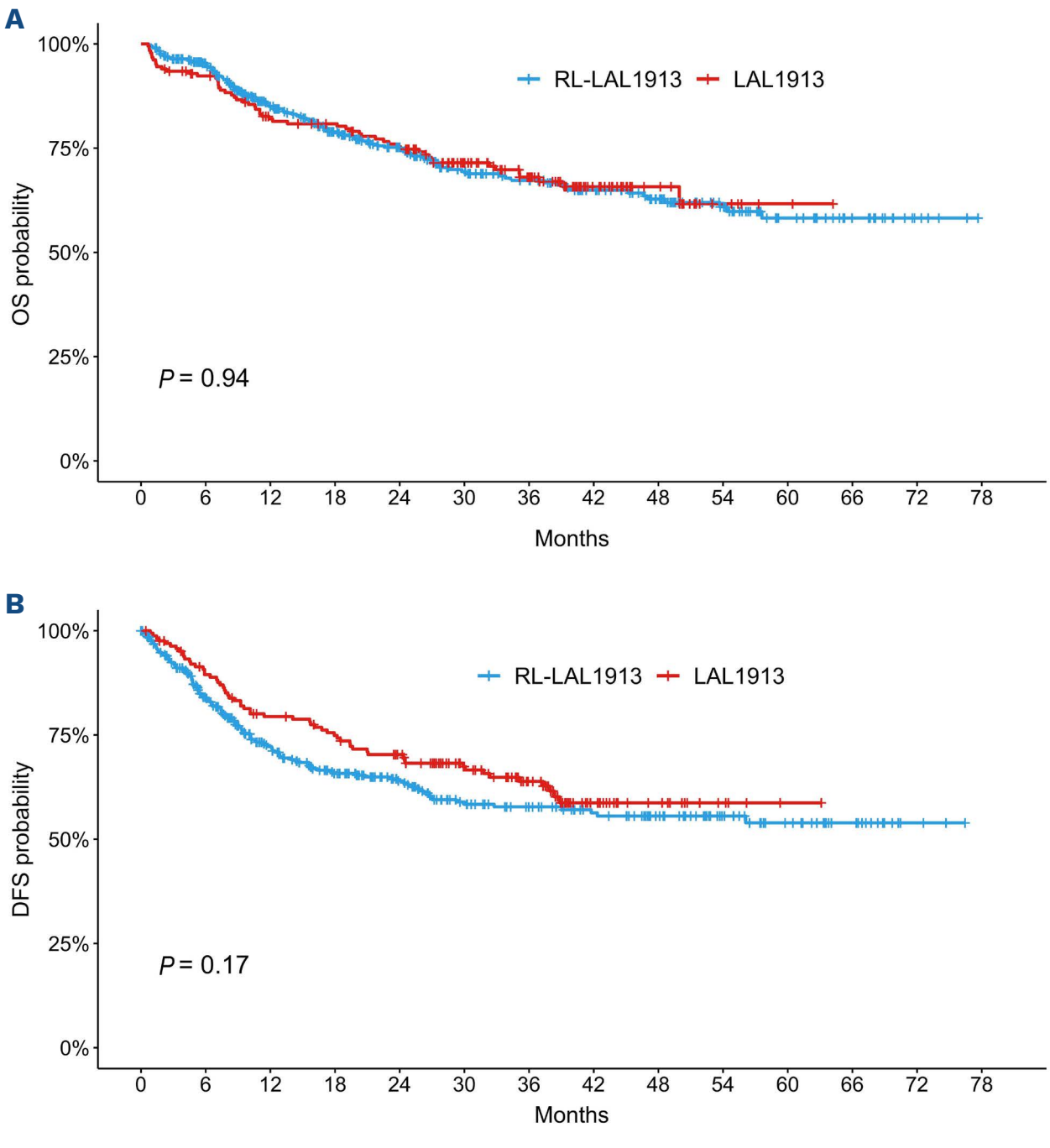


FIGURE 4. Comparison of overall survival (OS) and disease-free survival (DFS) between the study population and the GIMEMA LAL1913 clinical trial population. Overall survival (OS) and disease-free survival (DFS) in the real life study population (RL-LAL1913) (N=421) and the GIMEMA LAL1913 clinical trial population (LAL1913) (N=203).

LAL1913 clinical trial. Moreover, our analysis confirms the important role of HSCT in patients with high-risk factors or MRD positivity. Therefore, outside of clinical trials, efforts should be made to examine the disease characteristics in detail, keeping up with recently identified molecular subgroups, and to strictly monitor MRD at the appropriate timepoints to better identify patients with risk factors for early HSCT referral.[9,10]

A limitation of our study is that, for the majority of the patients, the Ph$^-$ like signature was not available; this should be more widely tested in standard clinical practice.[25-28] Furthermore, the widespread use of immunotherapy in patients with persisting pre-transplant MRD could improve transplant outcome. We are waiting for the results of the studies testing these approaches in patients with baseline high-risk features[29] or in all cases, including MRD-negative patients, where blinatumomab also appears to be effective.[30]

The tolerability of pegaspargase in the real-life setting remains an important concern, given the role of this drug as a cornerstone in the therapy regimen, and, indeed, our study is limited by the lack of a precise correlation analysis between pegaspargase dosage and response. Future studies are needed to personalize drug dosage for each patient according to tolerance, while remaining within the range of efficacy.[8,20,22,31,32] The widespread availability of asparaginase activity monitoring could help optimize dose calculation.[33]

A detailed analysis of infectious complications was beyond the scope of this study and will be detailed in a subsequent report. However, this remains an important issue to address, as infections are an important cause of morbidity and mortality, and efforts should be made to standardize anti-infectious prophylaxis, especially on the anti-mycotic front.[24,34]

Finally, elderly patients still show inferior outcomes compared to younger patients, even observing a median OS of 45 months. Future studies should aim at identifying the optimal age cut-off to define the “elderly”, and to design better and tailored induction therapies incorporating front-line immunotherapy to reduce toxicity and improve outcome.[35-37]

Disclosures

No conflicts of interest to disclose.

Contributions

AC designed the study (of which she is Principal Investigator), and wrote and revised the paper. DL collected data, performed the analysis, and wrote the paper. RF, CP, MC and SC collected data and helped revise the paper. All other authors collected data and approved the final manuscript.

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Data-sharing statement

Data regarding this research cannot be shared openly due to patient privacy concerns.

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