Received: 8 August 2022 | Accepted: 17 October 2022

DOI: 10.1111/bjh.18537

ORIGINAL PAPER

Incidence, treatment and outcome of central nervous system relapse in adult acute lymphoblastic leukaemia patients treated front-line with paediatric-inspired regimens: A retrospective multicentre Campus ALL study

Michelina Dargenio[1] | Massimiliano Bonifacio[2] | Sabina Chiaretti[3] | Antonella Vitale[3] | Nicola Stefano Fracchiolla[4] | Cristina Papayannidis[5] | Fabio Giglio[6] | Prassede Salutari[7] | Ernesta Audisio[8] | Barbara Scappini[9] | Patrizia Zappasodi[10] | Marzia Defina[11] | Fabio Forghieri[12] | Anna Maria Scattolin[13] | Elisabetta Todisco[14] | Monia Lunghi[15] | Fabio Guolo[16,17] | Maria Ilaria Del Principe[18] | Mario Annunziata[19] | Davide Lazzarotto[20] | Michele Cedrone[21] | Crescenza Pasciolla[22] | Annalisa Imovilli[23] | Ilaria Tanasi[2] | Silvia Trappolini[24] | Marco Cerrano[25] | Roberta La Starza[26] | Mauro Krampera[2] | Nicola Di Renzo[1] | Anna Candoni[19] | Giovanni Pizzolo[2] | Felicetto Ferrara[18] | Robin Foà[3]

[1]Ospedale Vito Fazzi, Unità Operativa di Ematologia e Trapianto, Lecce, Italy

[2]Dipartimento di Medicina, Sezione di Ematologia, Università e Azienda Ospedaliera Universitaria Integrata, Verona, Italy

[3]Divisione di Ematologia, Dipartimento di Medicina Traslazionale e di Precisione, Università Sapienza, Rome, Italy

[4]Unità Operativa di Ematologia, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]IRCCS Azienda Ospedaliero-Universitaria, Istituto di Ematologia "Seràgnoli", Bologna, Italy

[6]Ospedale San Raffaele, Unità Operativa di Ematologia, Milan, Italy

[7]Unità Operativa Complessa di Ematologia, Ospedale Civile Spirito Santo, Pescara, Italy

[8]Dipartimento di Ematologia e Oncologia, AO Città della Salute e della Scienza, Torino, Italy

[9]Unità Operativa di Ematologia, AOU Careggi, Florence, Italy

[10]Unità Operativa di Ematologia, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

[11]Unità Operativa Complessa di Ematologia, AOUS, Università di Siena, Siena, Italy

[12]Unità Operativa Complessa di Ematologia, AOU Policlinico, Modena, Italy

[13]Unità Operativa di Ematologia e Trapianto, Ospedale dell'Angelo, Mestre, Italy

[14]Unità Operativa Ematologia, Istituto Europeo di Oncologia (IEO), Milan, Italy

[15]Divisione di Ematologia, Dipartimento di Medicina Traslazionale, Università del Piemonte Orientale, Novara, Italy

[16]Clinica Ematologica, Dipartimento di Medicina Interna, Università degli Studi di Genova, Genoa, Italy

[17]Dipartimento di Oncologia e Ematologia, IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[18]Dipartimento di Biomedicina e Prevenzione, Università degli studi Tor Vergata, Rome, Italy

[19]Unità Operativa Complessa di Ematologia, AORN Cardarelli, Naples, Italy

[20]Clinica ematologica e centro trapianti, Azienda sanitaria universitaria Friuli Centrale, Udine, Italy

Abbreviations: ALL, Acute Lymphoblastic Leukemia; ARA-C, cytarabine; AIRC, Associazione Italiana Ricerca sul Cancro; BM, bone marrow; CAR-T, chimaeric antigen receptor-engineered T-cells; CC, conventional cytology; CHT, chemotherapy; CI, confidence interval; CNS, Central Nervous System; CR, complete remission; CSF, cerebrospinal fluid; CSI, cranial spinal irradiation; CT, computed tomography; FCM, flow cytometry; HD, high dose; HR, hazard ratio; HR, high risk; HSCT, haematopoietic stem cell transplant; IRB, Internal Review Board; IT, intrathecal; LDH, lactate dehydrogenase; MRD, minimal residual disease; MRI, magnetic resonance imaging; MTX, methotrexate; OCNSD, occult CNS disease; OS, overall survival; Ph, Philadelphia; PRIN, Progetti di Rilevante Interesse Nazionale; RT, radiotherapy; SE, standard error; SR, standard risk; TBI, total body irradiation; TKI, tyrosine kinase inhibitors; VHR, very high risk; WBC, white blood cell.

Michelina Dargenio and Massimiliano Bonifacio contributed equally to this work.

[21]Unità Operativa Complessa di Ematologia, Ospedale San Giovanni Addolorata, Rome, Italy

[22]Unità Operativa di Ematologia, IRCCS Istituto Tumori Giovanni Paolo II, Bari, Italy

[23]Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

[24]Unità Operativa di Ematologia, AOU- Ospedali Riuniti, Ancona, Italy

[25]Unità Operativa di Ematologia, Presidio Molinette-AOU Città della Salute e della Scienza, Torino, Italy

[26]Sezione di Ematologia e Trapianto, Università degli Studi di Perugia, A.O. Perugia, Italy

Correspondence
Michelina Dargenio, Unità Operativa di Ematologia e Trapianto, Ospedale Vito Fazzi, Lecce, Italy.
Email: miviforina@tiscali.it

Robin Foà, *"Sapienza"* University of Rome, Rome, Italy.
Email: rfoa@bce.uniroma1.it

Summary

Within the Campus ALL network we analyzed the incidence, characteristics, treatment and outcome of a central nervous system (CNS) relapse in 1035 consecutive adult acute lymphoblastic leukemia (ALL) patients treated frontline with pediatric-inspired protocols between 2009 and 2020. Seventy-one patients (6.8%) experienced a CNS recurrence, more frequently in T- (28/278; 10%) than in B-ALL (43/757; 5.7%) ($p = 0.017$). An early CNS relapse—< 12 months from diagnosis—was observed in 41 patients. In multivariate analysis, risk factors for early CNS relapse included T-cell phenotype ($p = <0.001$), hyperleucocytosis $>100 \times 10^9$/L ($p<0.001$) and male gender ($p = 0.015$). Treatment was heterogeneous, including chemotherapy, radiotherapy, intrathecal therapy and novel agents. A complete remission (CR) was obtained in 39 patients (55%) with no differences among strategies. After CR, 26 patients underwent an allogenic transplant, with a significant overall survival benefit compared to non-transplanted patients ($p = 0.012$). After a median observation of 8 months from CNS relapse, 23 patients (32%) were alive. In multivariate analysis, the time to CNS relapse was the strongest predictor of a lower 2-year post-relapse survival ($p<0.001$). In conclusion, in adult ALL the outcome after a CNS relapse remains very poor. Effective CNS prophylaxis remains the best approach and allogenic transplant should be pursued when possible.

KEYWORDS
adult ALL, CNS relapse, paediatric-like regimens

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is the most common tumour in children and is considered a therapeutic success in cancer with five-year event-free survival rates of approximately 85% and overall survival (OS) rates around 90%.[1] At present, highly effective paediatric-based regimens warrant five-year survival rates of about 60% in adolescents and young adult patients.[2,3] In view of these data, a similar approach has been progressively extended to older patients, with improved results up to 55 years of age.[4,5] Nevertheless, relapse remains the main cause of treatment failure.

The central nervous system (CNS) is the most common site of extramedullary involvement in ALL.[6] CNS involvement at diagnosis of ALL is detected in 5%–25% of cases.[6–9] Despite the intrathecal (IT) administration of prophylactic chemotherapy and the use of high-dose systemic methotrexate and/or cytarabine as part of the consolidation treatment,[10,11] CNS relapse occurs in 7%–15% of adult ALL patients[9,12–14] and, unlike in children, it usually occurs within the first year from diagnosis.[12,13,15] Although isolated CNS relapses do occur, recurrence of ALL within the CNS usually coincides with or predicts a systemic relapse in the bone marrow (BM) and blood soon after.[12,15] Risk factors at diagnosis related to subsequent CNS relapse are: T-cell immunophenotype, the presence of high-risk cytogenetic abnormalities [*t*(4;11), *t*(9;22)], hyperleukocytosis (above 100×10^9/L) and an overt CNS leukaemia at diagnosis.[16]

The optimal management of CNS relapse with or without a concurrent BM involvement remains uncertain.[17] Treatment options include the use of many of the same chemotherapy agents used up-front at concentrations capable of crossing the blood–brain barrier, and partly novel immunotherapies — namely blinatumomab and inotuzumab ozogamicin — after CNS sterilization with IT chemotherapy. Allogeneic haematopoietic stem cell transplant (HSCT) is considered the gold standard for relapsed ALL patients who achieve a second remission. However, there is no standard approach to effectively reduce the rate of further CNS relapses and to improve survival after

transplantation. Strategies to improve outcome include total body irradiation (TBI) in the conditioning regimen, cranial spinal irradiation (CSI) and cranial radiotherapy (RT), or IT chemotherapy in the peritransplant setting.[18,19] The impact on outcome of intensified conditioning with TBI and CNS RT is still undetermined.[17]

To address these questions on a contemporary series of patients in the framework of the Campus ALL network, we conducted this retrospective study analysing the incidence, characteristics, treatment and OS of CNS relapse in adult ALL patients treated front-line with paediatric-inspired and minimal residual disease (MRD)-oriented therapy.

MATERIALS AND METHODS

This is a multicentre retrospective analysis that included all adult patients (age ≥18 years) with a diagnosis of *de novo* ALL treated with paediatric-inspired regimens at 25 Italian haematology centres between 2009 and 2020. Paediatric-inspired regimens included one of the following protocols: NILG 10/07, AIEOP 2000, GIMEMA LAL1308 and GIMEMA LAL1913.[20–23] Patients were either included in the original studies or treated according to the same protocols in clinical practice. Philadelphia chromosome (Ph)-positive ALL patients were included if treated with tyrosine kinase inhibitors (TKI) in addition to one of the above-mentioned protocols. All regimens included CNS prophylaxis during induction and consolidation with systemic high-dose chemotherapy [methotrexate(MTX)/arabinosyl cytarabine (ARA-C)] and IT chemotherapy with MTX with/without ARA-C and steroids during all treatment phases.[20–23] No patient received RT or CSI as part of their initial treatment. Risk classification at diagnosis was based on previously reported definitions.[24–26] Patients with very high-risk (VHR) features or classified as high or standard risk and with a positive MRD status at the end of induction/early consolidation were allocated to front-line HSCT, if suitable.

Patients with a CNS involvement at relapse — including also those with a CNS involvement at initial presentation who obtained a complete remission (CR) and then relapsed — represent the study population for this analysis. Patients' records were retrospectively collected for their clinical and laboratory characteristics, treatment regimens and outcome after CNS recurrence in an anonymous database.

All patients provided informed consent for the participation in studies on their disease and for the collection of data according to the protocol used in the clinical practice. This retrospective study was approved by the Internal Review Board (IRB) of the coordinating centre, in accordance with the Helsinki Declaration.

The definition of CNS involvement included one or more of the following: (a) evidence of leukaemic blasts in the cerebrospinal fluid (CSF) by conventional cytology (CC) and/or flow cytometry (FCM), or (b) contrast-enhancing brain or spinal mass on imaging attributed to leukaemic involvement. CC positivity was defined as unequivocal morphologic evidence of leukaemic blasts in the CSF and/or a CSF white blood cell (WBC) count of 5/μl or higherwith less than 10 erythrocytes/μl.[27,28]

FCM positivity was defined by the presence in CSF of 10 or more phenotypically abnormal events, forming a cluster.[9,29] All patients with evidence of a CNS relapse underwent a BM examination. Relapse events were defined by the time from initial diagnosis: early, less than12 months; late, at least 12 months, also in keeping with the current literature,[12,13,15] and site: (i) isolated CNS relapse; (ii) concomitant CNS and BM relapse; or (iii) concomitant CNS and molecular BM relapse (BM MRD+). A BM recurrence within four weeks from the detection of CNS disease was considered as a systemic recurrence.

Survival was considered from the date of the first CNS recurrence to the date of death or the last follow-up. CR duration was considered from the date of CR achievement after the first CNS recurrence to the date of further relapse at any site or the last follow-up.

Survival and CR duration distributions were estimated using the Kaplan–Meier method and were compared using the log-rank test. Comparisons between groups were performed to assess differences in clinical data using Fisher's exact test for categorical variables. All tests were two-sided, accepting $p < 0.05$ as indicating a statistically significant difference, and confidence intervals (Cis) were calculated at the 95% level. Multivariate analysis was performed using a Cox model after the proportional hazard assumption was checked. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Among 1035 consecutive newly diagnosed adult ALL (B-lineage 757, T-lineage 278), we identified a total of 71 patients (6.8%) who experienced a CNS relapse.

Patient population

The characteristics at disease onset of patients who later experienced a CNS relapse are summarized in Table 1. Median age was 35 years (range 18–64) and 50 (70.4%) were male. Median WBC value was 35.9×10^9/L (range 1.7–248).

Overall, a CNS relapse was significantly more frequent in T-ALL (28/278; 10%) than in B-ALL (43/757; 5.7%) ($p = 0.017$). Cytogenetic analysis was available for 66 patients (93%): 12 patients (22.5%) had a complex karyotype, including four patients who were also Ph+, nine patients (21% of B-ALL) were Ph+, one patient had a t(4;11)/*KMT2A* rearrangement at 11q23; one patient had a t(1;19)/*E2A/PBX1* alteration. Within B-lineage ALL patients devoid of major molecular lesions ($n = 32$), the Ph-like predictor was tested in 13, and six (46%) proved Ph-like.[30]

TABLE 1 Patients' characteristics at diagnosis

	Overall (n = 71)
Age (years), median (range)	35 (18–64)
Sex, *n* (%)	
Male	50 (70.4%)
Female	21 (29.6%)
Risk class, *n* (%)	
SR	19 (26.7%)
HR	10 (14.1%)
VHR	42 (59.2%)
WBC (10^9/L), median (range)	35.9 (1.7–248)
WBC×10^9/L, *n* (%)	
0–30	36 (50.7%)
30–100	16 (23.5%)
>100	17 (25.0%)
Missing	2
Immunophenotype, *n* (%)	
B-ALL	43 (60.6%)
Common/pre-B	41 (95.3%)
Pro-B	2 (4.7%)
T-ALL	28 (39.4%)
Cortical-T	13 (46.4%)
Pre−/mature-T	15 (53.6%)
Cytogenetics/molecular genetics, *n* (%)	
Non adverse/normal	39 (55%)
Adverse	27 (38%)
Ph+	5 (18.5%)
t(4;11)	1 (3.7%)
Other	21 (77.7%)
Missing	5 (7%)
Other localization, *n* (%)	
CNS	7 (9.9%)
Mediastinum	16 (22.5%)
Liver	6 (8.5%)
Spleen	19 (26.8%)
Other	23 (32.4%)
LDH (U/L), median (range)	1112 (200–9860)

Abbreviations: CNS, central nervous system; HR, high risk; LDH, lactate dehydrogenase; Ph, Philadelphia; SR, standard risk; VHR, very high risk; WBC, white blood cell.

A mediastinal mass was present in 16 patients (22.5%), 14 being T-ALL; a testicular involvement was found in four of 50 males (8%). Seven patients (9.9%) also had a CNS involvement at the initial presentation.

As a result of these characteristics, 42 patients (59.2%) were classified as VHR, 10 (14.1%) as high risk and 19 (26.7%) as standard risk.

Front-line treatment and response

The initial treatment protocol was as follows: GIMEMA LAL1913/GIMEMA LAL1913-inspired in 27 patients (38%), NILG10/07 ALL in 25 (35.2%), GIMEMA LAL1308 in 11 (15.5%) and AIEOP 2000 in eight (11.3%). All patients obtained a CR after induction therapy. Twenty-nine patients (41%) also achieved a complete MRD response, while 26 (36.5%) remained MRD-positive and 16 (22.5%) had an unknown MRD status. After consolidation, the rate of MRD negativity increased to 63%. The median number of prophylactic IT administrations was eight (range 4–13), lower than planned in the original protocols due to the rather high occurrence of early CNS relapse, while the median number of therapeutic IT administrations in patients with a CNS involvement at diagnosis was six (range 1–18). Overall, the median time from diagnosis to the first IT was six days (range 1–55). The median dose of MTX administered was 3 g/m^2 (range 1.5–5) varying according to the immunophenotype. A HSCT was performed as part of the initial treatment programme (i.e. before CNS relapse) in 18 patients (25.3%) after a median time of eight months from diagnosis (range 3–24).

Characteristics of CNS relapses and risk factors for early CNS relapse

The median time to CNS relapse was 10 months (range 1–46). The median number of therapeutic lines administered prior to the CNS relapse was one (range 1–6) and 45/71 patients (63%) experienced a CNS relapse after the first line of treatment. Sixteen patients (22.5%), all without CNS involvement at diagnosis, were treated with immunotherapy prior to the CNS relapse for MRD positivity or systemic relapse: nine patients (13%) received blinatumomab, two (3%) received inotuzumab ozogamicin and five (7%) received both agents. Twenty-four patients (34%) underwent a HSCT before their first CNS relapse.

At CNS relapse, 44 patients (62%) had neurological symptoms: 24 (34%) had a facial paralysis, 10 (14%) had diplopia/visual impairment and 10 (14%) had intracranial hypertension. The diagnosis of CNS relapse was made by CC and/or immunophenotypic evidence of leukaemic blasts in the CSF in 43 patients (60.5%), by positive MRI/CT scan in seven (9.9%) and by a concomitant positive CSF and MRI/CT scan in 21 (29.5%).

Forty-one patients (58%) had an early CNS relapse and 30 (42%) had a late CNS relapse. Regarding the site of relapse, 41 patients (58%) experienced an isolated CNS relapse, 21 (29%) had a concomitant BM involvement and nine (13%) had a concomitant BM MRD+.

A univariate analysis of risk factors associated with early relapse did not show any significant correlation with age, risk class, cytogenetics/molecular genetics, Ph-like status, other extramedullary localizations (including CNS involvement at

diagnosis), lactic dehydrogenase level, dose of MTX, number of prophylactic/therapeutic IT and MRD status at the end of induction. Conversely, male gender (p = 0.015), T-precursor immunophenotype (p <0.001) and hyperleukocytosis (WBC >100×10^9/L) for both B- and T- cell phenotypes (p <0.001) were significantly associated with a greater risk of early CNS relapse both in univariate and multivariate analysis (Table 2).

Treatment of CNS relapse and outcome

Treatment of CNS relapse was heterogeneous, including a combination of systemic chemotherapy, RT, IT, TKIs and novel agents, as reported in Table 3. Overall, systemic chemotherapy was used in 51 patients and included: HD-MTX with or without HD-ARA-C (34/51; 67%), FLAI/FLAG (11/51; 21%), HD-ARA-C (4/51; 8%), nelarabine (1/51; 2%) and clofarabine/cyclophosphamide (1/51; 2%). A CR was obtained in 39 patients (55%). No treatment modality was associated with a statistically superior CR rate compared to the others (p = 0.538). Of note, five out of six patients with a concurrent CNS and systemic relapse who were treated with immunotherapy (three blinatumomab, three inotuzumab ozogamicin) after clearance of CNS involvement by multiple IT obtained a CR. After CR2 achievement, 26 patients (37%) underwent a HSCT. Twenty-one patients (29%) never underwent a transplant.

After a median follow-up of eight months from CNS relapse, 23 patients (32%) were alive, 22 remaining in CR. The deaths were due to CNS relapse in 45 patients (94%) and due to infectious complications in three patients (6%). The median OS from the first CNS relapse was 8.5 months [95% confidence interval (CI): 6–14] (Figure 1A). The median OS in early and late CNS relapse was six months (95% CI: 3–8) and 14 months (95% CI: 8.0–20.0), respectively (p <0.001) (Figure 1B). The median OS after isolated CNS relapse, CNS plus concomitant BM MRD+ relapse and CNS plus concomitant haematologic relapse was 14 (95% CI: 8–20), 12.5 (95% CI: 1–22) and five (95% CI: 1–7) months, respectively (p = 0.03) (Figure 1C). The estimated five-year survival rate was only 5.6%.

HSCT was associated with a statistically significant OS benefit compared to non-transplanted patients (p = 0.012). The median OS of patients for whom the transplant was performed as consolidation therapy was 11 months (95% CI: 6–23) vs. 5.5 months for patients with a post-transplant CNS relapse (95% CI: 1–22) and five months for patients who never underwent a transplant (95% CI: 1–8). Notably, 11 of the 26 patients (42%) who were transplanted after the CNS relapse experienced a further CNS relapse. All patients who underwent a HSCT received myeloablative conditioning and the preparation regimen was TBI-based in 12/26 patients (46%). Additionally, four patients received CSI (18–20 Gy). The use of TBI as part of the conditioning regimen, did not affect OS when compared with that of no TBI-based regimen (p = 0.105).

A univariate analysis of risk factors associated with a two-year OS after CNS relapse identified T-precursor immunophenotype (p = 0.05), hyperleukocytosis >100×10^9/L at initial diagnosis (p = 0.038), no transplant as consolidation therapy after CNS relapse (p = 0.035) and early relapse (p <0.001) as significant predictors of worse OS. In multivariate analysis, only early relapse remained predictive of a worse OS [hazard ratio (HR) = 26.717, 95% CI: 3.639–196.145, p <0.001] (Table 4).

DISCUSSION

Despite the much-improved successes in the overall management of adult ALL, survival in patients with a CNS relapse after front-line treatment remains poor. Few reports have analysed the impact of contemporary ALL regimens on the outcome of adult patients with CNS recurrence.[9,12,14,15] The incidence of CNS recurrence varied by phenotype and genotype. In our study - one of the largest published series - the frequency of CNS recurrence (6.8%) is in line with the literature. As in other adult ALL studies, most CNS relapses (58%) occurred within the first year from diagnosis, unlike in children.[12,13,15] In one of the largest and most recent dataset on Ph-negative B-precursor relapsed/refractory adult ALL (extramedullary relapses were not included),[31] more than half of the relapses were detected within one year from diagnosis, during ongoing intensive treatment. These observations suggest that it might be appropriate to consider a different definition of early and late relapse in adults, bringing the cut-off to 12 months or even earlier as compared to the standard cut-off in the paediatric population, which is typically set at 18 months.

In line with the literature, CNS relapse was significantly more frequent in T-ALL (10%) than in B-ALL (5.7%).[32] Interestingly, among patients with B-cell precursor-ALL devoid of major molecular lesions, 46% of tested patients were Ph-like. The molecular analysis of these cases, known to confer poor prognosis,[30,33,34] identified rare cytogenetic subtypes which may also be associated with a particular risk of CNS infiltration,[35,36] such as the *ETV6-NTRK3* rearrangements.[36,37] Likewise, time to CNS relapse remains the strongest predictor of OS,[14,38] with early CNS relapse patients having a particularly poor outcome. The risk factors for early CNS relapse identified in this series - T-cell immunophenotype, hyperleukocytosis, male gender - are in agreement with the literature.[16,38] These higher-risk groups might benefit from more aggressive CNS prophylaxis. In the current Italian trial for Ph + ALL (LAL2820, clinicaltrials gov. Identifier: NCT04722848), the number of lumbar punctures has been increased to 15 for an unexpectedly rather high incidence of CNS involvement observed in the induction-consolidation chemotherapy-free LAL2116 (D-ALBA) trial.[39,40] The absence of chemotherapy might have favoured this condition, in spite of the use of dasatinib, known to overcome the blood–brain barrier. Further investigations are needed to verify whether an increase in the number of lumbar punctures will have

TABLE 2 Univariate and multivariate analyses of risk factors associated with early relapse

	Early relapses	Late relapses	Overall	*p* value	
	(*n* = 41)	(*n* = 30)	(*n* = 71)	Univariate	Multivariate[a]
Age (Mean/sd)	36.63 (13.49)	35.33 (14.26)	36.08 (13.73)	0.696	—
Sex, *n* (%)					
Male	33 (80.5%)	17 (56.7%)	50 (70.4%)	0.038	0.015
Female	8 (19.5%)	13 (43.3%)	21 (29.6%)		
Risk class					
SR	7 (17.1%)	12 (40.0%)	19 (26.7%)	0.382	—
HR	7 (17.1%)	3 (10.0%)	10 (14.1%)		
VHR	27 (65.8%)	15 (50.0%)	42 (59,2%)		
WBC, $\times 10^9$/L					
0–30	17 (41.5%)	19 (63.4%)	36 (50.7%)		
30–100	6 (14.6%)	10 (33.4%)	16 (22.5%)		
More than 100	16 (39.0%)	1 (3.2%)	17 (23.9%)	<0.001	<0.001
Missing	2 (4.8%)	0 (0%)	2 (2.8%)		
Immunophenotype				0.017	—
B-ALL	18 (43.9%)	25 (83.3%)	43 (60.6%)	0.012	—
Common/pre-B	17 (94.4%)	24 (96.0%)	41 (95.3%)		
Pro-B	1 (5.6%)	1 (4.0%)	2 (4.7%)		
T-ALL	23 (56.1%)	5 (16.7%)	28 (39.4%)	0.006	<0.001
Cortical-T	12 (52.2%)	1 (20.0%)	13 (46.4%)		
Pre-/mature-T	11 (47.8%)	4 (80.0%)	15 (53.6%)		
Cytogenetics/molecular genetics				0.262	—
Non-adverse/normal	26 (63.4%)	13 (43.3%)	39 (55%)		
Adverse	13 (31.7%)	14 (46.6%)	27 (38%)	0.904	—
Ph+	1 (7.7%)	4 (28.6%)	5 (18.5%)		
t(4;11)	1 (7.7%)	0 (0.0%)	1 (3.7%)		
Other	11 (84.6%)	10 (71.4%)	21 (77.7%)		
Missing	2 (4.8%)	3 (10%)	5 (7%)		
Other localization					
CNS	4 (9.8%)	3 (10.0%)	7 (9.9%)	1.000	—
Mediastinum	12 (29.3%)	4 (13.4%)	16 (22.5%)	0.154	—
Liver	4 (9.8%)	2 (6.7%)	6 (8.5%)	1.000	—
Spleen	11 (26.8%)	8 (26.7%)	19 (26.8%)	1.000	—
Other	10 (24.4%)	13 (43.4%)	23 (32.4%)	1.000	—
LDH (U/L), mean (sd)	2075.11 (2391.84)	1464.39 (1691.87)	1812.03 (2125.67)	0.255	—
Dose MTX (gr/m^2), mean (sd)	3.16 (1.54)	3.19 (1.61)	3.18 (1.56)	0.941	—
IT prophylactic/therapeutic (mean/sd)	6.25 (1.71)	10.00 (5.20)	7.86 (3.80)	0.224	—
MRD (end of induction)					
MRD pos	15 (36.6%)	11 (36.7%)	26 (36.6%)	0.680	—
MRD neg	16 (39.0%)	13 (43.3%)	29 (40.8%)		
MRD unknown	10 (24.4%)	6 (20.0%)	16 (22.5%)		
Ph-like					
Yes	2 (4.9%)	4 (13.3%)	6 (8.5%)	0.797	—
No	3 (7,3%)	4 (13.3%)	7 (9.9%)		

Abbreviations: ALL, acute lymphoblastic leukaemia; CNS, central nervous system; HR, high risk; IT, intrathecal; LDH, lactate dehydrogenase; MRD, minimal residual disease; MTX, methotrexate; neg, negative; Ph, Philadelphia; Ph-like, Philadelphia-like; pos, positive; SR, standard risk; VHR, very high risk; WBC, white blood cell.

[a]Stepwise backward selection method is developed for the analysis.

an impact on the rate of CNS relapses, and specifically of early relapses.

Recently, several published experiences demonstrated the superior sensitivity of FCM over CC for the detection of CNS disease, contributing to establish a new standard, the so-called "occult CNS disease" (OCNSD), i.e. FCM positivity and CC negativity.[29,41,42] In the framework of the national Campus ALL programme, we conducted a multicentre retrospective study which confirmed the superior sensitivity of FCM and highlighted the adverse outcome associated with OCNSD.[9] In the present study, FCM on CSF was carried out in 90% of patients highlighting how FCM has in Italy already entered the work-up of ALL at diagnosis and during the follow-up. Furthermore, as in other studies, many cases of CNS relapse (42%) preceded a systemic relapse and adults with CNS recurrence and a combined BM relapse have a particularly poor prognosis.[12,15] At the time of CNS relapse, a BM morphological evaluation alone is not enough and a BM MRD assessment is warranted, since the OS of patients with a concurrent CNS and BM MRD+ relapse is inferior to that of patients with an isolated CNS involvement.

Collectively, our data, with a median OS from relapse of 8.5 months, are better than those of previous reports, in particular for isolated CNS relapse which is 14 months compared to the six months reported before the year 2000.[12] Considering the nature of this retrospective study, we do

TABLE 3 Modality of treatment of CNS relapse and CR rate

	Number of patients (%)	CR rate *N*, (%)
All patients	71 (100)	39 (55)
CHT + IT	31 (44)	13 (42)
CHT + RT + IT	17 (24)	12 (70)
RT + IT	9 (13)	5 (55)
Immunotherapy + IT	6 (8)	5 (83)
TKI + IT	5 (7)	3 (60)
CHT	3 (4)	1 (33)

Abbreviations: CR, complete remission; CHT, chemotherapy; IT, intrathecal; RT, radiotherapy; TKI, Tyrosine kinase inhibitors.

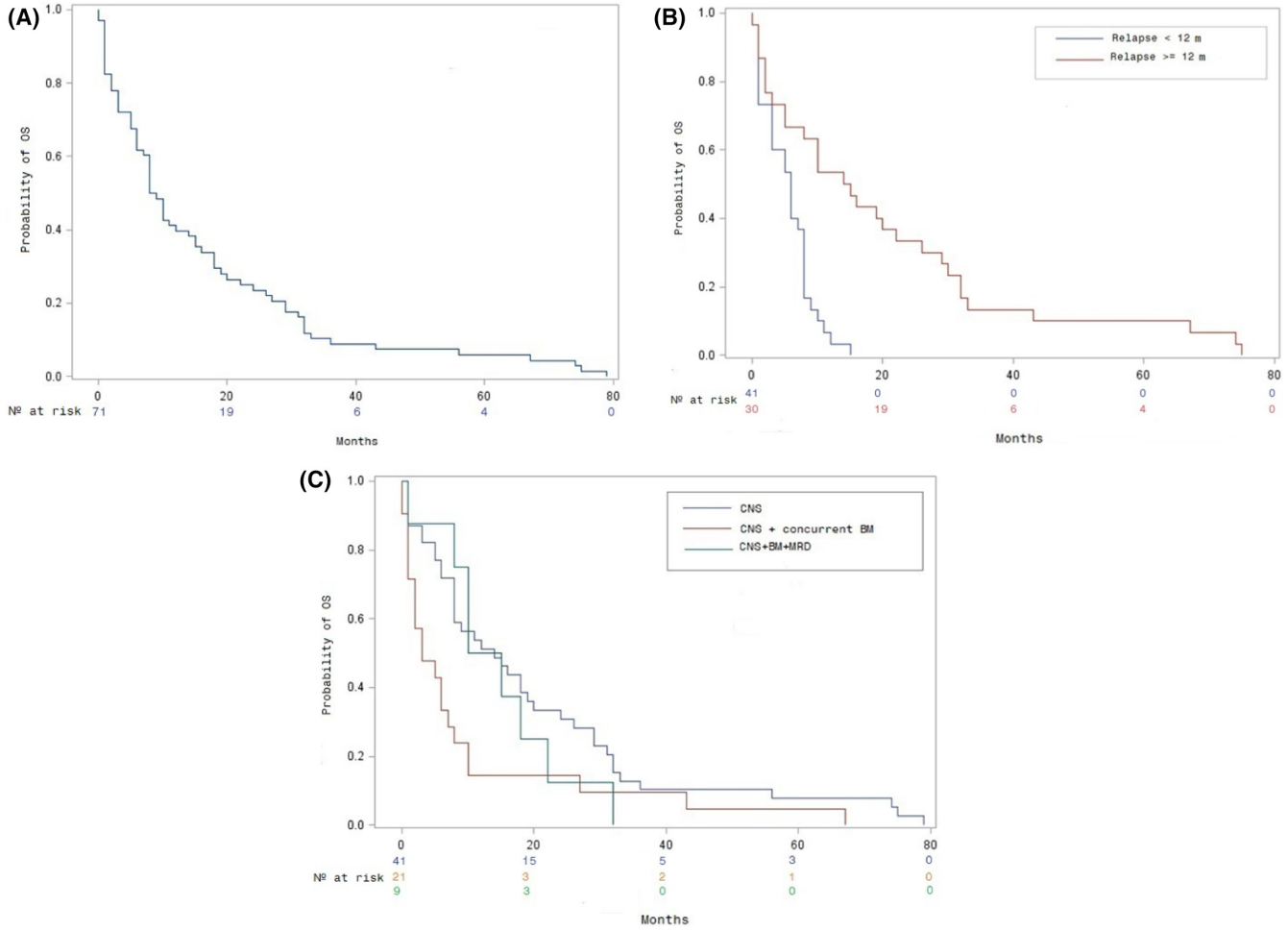

FIGURE 1 (A) Overall survival (OS) of the whole population (71 cases) from the first central nervous system (CNS) relapse. Median OS was 8.5 months [95% CI:6–14]. (B) OS from CNS relapse by time from initial diagnosis (early <12 months; late ≥12 months). The median OS in early and late CNS relapse was six months (95% CI:3–8) and 14 months (95% CI:8.0–20.0) respectively ($p < 0.001$). (C) OS from CNS relapse by site of relapse. Median OS after isolated CNS relapse, CNS plus concomitant bone marrow (BM) minimal residual disease (MRD)-positive relapse and CNS plus concomitant haematologic relapse was 14 (95% CI:8–20), 12.5 (95% CI:1–22) and 5 (95% CI:1–7) months respectively ($p = 0.03$). [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Univariate and multivariate analyses of risk factors associated with 2-year OS after CNS relapse

	N	Survival time (mean ± SE)	Two-year survival hazard rate (95% CI)	*p* value	
				Cox univariate	Cox multivariate[a]
Age (mean/sd)	71	16.33 ± 1.97[b]	1.024 (0.997–1.052)	0.086	—
Sex					
Male	50	11.41 ± 1.04	0.617 (0.136–2.801)	0.364	—
Female	21	8.62 ± 0.92	0.421 (0.096–1.844)		
Risk class					
SR	19	11.81 ± 1.13	0.716 (0.291–1.757)	0.202	—
HR	10	5.21 ± 0.44	0.642 (0.248–1.662)		
VHR	42	5.33 ± 0.87	1.412 (0.531–3.111)		
WBC, $\times 10^9$/L					
0–30	36	9.14 ± 0.88	0.827 (0.341–0.721)	0.038	0.321
30–100	16	5.67 ± 0.32	0.769 (0.253–0.924)		
More than 100	17	2.22 ± 0.12	2.209 (0.459–4.187)		
Immunophenotipe					
Common/pre-B	41	13.93 ± 1.05	1.007 (0.132–1.701)	0.05	0.288
Pro-B	2	NC	1.699 (0.106–27.185)		
Cortical-T	13	6.48 ± 1.46	2.924 (0.356–23.807)		
Pre–/mature-T	15	6.33 ± 0.87	2.154 (0.273–17.086)		
Cytogenetics/molecular genetics					
Non adverse/normal	39	NC	NC	NC	—
Adverse	27	NC	NC		—
MRD (end of induction)					
MRD pos	26	9.67 ± 0.43	1.025 (0.185–5.683)	0.066	—
MRD neg	29	10.45 ± 0.90	0.937 (0.248–3.548)		
MRD unknown	16	11.17 ± 0.94	0.399 (0.126–1.265)		
Ph-like					
Yes	6	2.12 ± 0.29	1.210 (0.322–3.622)	0.412	—
No	7	12.01 ± 0.86	0.532 (0.177–1.944)		
Time to relapse					
Early relapse	41	1.00 ± NC	26.717 (3.639–196.145)	<0.001	<0.001
Late relapse	30	8.99 ± 1.04	0.116 (0.104–0.319)		
TBI					
Yes	11	11.69 ± 0.99	0.992 (0.378–2.605)	0.986	—
No	15	8.22 ± 0.80	1.008 (0.384–2.647)		
Transplant post-relapse					
Yes	26	12.17 ± 0.76	0.461 (0.222–0.957)	0.035	0.111
No	45	5.48 ± 0.52	2.170 (1.045–4.508)		
CNS					
Isolated CNS	41	15.43 ± 1.90	1.036 (0.412–2.722)	0.671	—
CNS + concurrent BM	21	5.08 ± 0.62	2.122 (0.408–9.812)		
CNS + molecular BM	9	10.15 ± 0.94	0.322 (0.017–4.092)		

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system; CR, HR, high risk; MRD, minimal residual disease; NC, not calculated; neg, negative; OS, overall survival; Ph-like, Philadelphia-like; pos, positive; SE, standard error; SR, standard risk; TBI, total body irradiation; VHR, very high risk; WBC, white blood cell.

[a]Backward selection method.

[b]Value at baseline.

not know if the improved outcome of isolated CNS relapses might be attributed to a more refined and early diagnosis of CNS disease, to the use of paediatric-like regimens, to the use of asparaginase and/or to new therapeutic strategies. Most, but not all (e.g. HyperCVAD), adult ALL regimens include native asparaginase or pegylated asparaginase. While it is well established that systemic asparaginase lowers asparagine levels in the CNS, it is uncertain whether this provides any additional benefit to prevent CNS dissemination.[43] Recent paediatric studies have reported discordant results.[44,45] In our series, all patients received asparaginase: further analyses on the doses administered and interruptions are warranted.

The management of adults with ALL and CNS recurrence is not standardized and little progress has been made over the years.[17] Treatments for re-induction of relapsed ALL primarily involve many of the same traditional chemotherapy agents (eg. HD-MTX, HD-ARA-C),[10,11,17] with a partial benefit in preventing or eradicating CNS involvement. Furthermore, the prognosis of CNS relapse is poor also for the tendency to further relapses.[12,17] In our cohort, treatments were heterogeneous, including systemic chemotherapy, RT, IT, TKI and novel agents. No treatment modality was associated to a superior CR rate compared to the others. Although 55% of our population achieved a CR after CNS recurrence, 28% had a further relapse. The impact of newer immunotherapeutic approaches with agents such as blinatumomab, inotuzumab ozogamicin, or chimaeric antigen receptor-engineered T-cells (CAR-T) in the management of patients with CNS with or without concurrent BM relapse remains to be determined.[46,47] With the limitations of the sample size, in our group 16 B-ALL patients (37%) were treated prior to the CNS relapse with immunotherapy — blinatumomab or inotuzumab ozogamicin — and six received these agents post-relapse. Notably, all six Ph-like ALL patients had received previous immunotherapy and one of them had a CNS relapse also after CAR-T-cell therapy, suggesting a neurotropism of this subtype; noteworthy, the combination of ruxolitinib with chemotherapy resulted in a molecular remission in a high-risk Ph-like refractory patient with a macroscopic CSF involvement.[48]

In our study, as well as in others,[18,49] HSCT represented the most effective therapeutic option with a significant OS benefit compared to patients who relapsed after a previous transplant or who could never undergo a transplant (p = 0.012). Even if HSCT represents the treatment of choice for VHR patients, in this series it was performed as part of the initial treatment programme only in 18 patients (25.3%) and after a relatively long median time from diagnosis (8 months, range 3–24), despite the fact that 59.2% of the entire cohort was classified as VHR. Noteworthy, 42% of patients had a further CNS relapse after transplant. The exclusion of prophylactic RT from the therapeutic backbone in ALL[12,15,16] may not only protect patients from its secondary side effects, but also offer the possibility to include full-dose TBI as a salvage therapy for patients with an isolated CNS relapse.

However, in our series the use of TBI as part of the conditioning regimen did not provide a survival benefit, suggesting that the graft-versus-leukaemia effect is probably the dominant factor involved in leukaemia control in the CNS after a HSCT.[18,19,50] Further prospective studies on larger series are needed to confirm these data.

In conclusion, in the era of paediatric-like and MRD-driven regimens, the outcome after a CNS relapse remains very poor and effective CNS prophylaxis in adult patients with ALL remains the best approach to address CNS recurrence and, ideally, should be personalized to the risk of CNS relapse. Our findings, though limited by the retrospective nature of the cohort analysed, indicate that hyperleukocytosis, male gender, T-lineage ALL and a Ph-like signature could be predictive factors of CNS recurrence, with early relapse being the only independent prognostic factor of survival after CNS recurrence in multivariate analysis. A potential strategy to overcome relapse is to increase CNS prophylaxis through a greater number of IT procedures and by using a triple combination [MTX, ARA-C and steroids] to these cases. This study confirms that HSCT represents the best option to prolong survival and should be pursued as soon as possible, though further efforts are needed to prevent the risk of post-transplant CNS relapse. Finally, efforts are currently underway to clarify if certain biologic features may be associated with a predisposing neurotropism in ALL, as already documented in blastic plasmacytoid dendritic cell neoplasms with a CNS dissemination.[51]

ACKNOWLEDGEMENTS

The authors would like to thank all participants of the Campus ALL and Andrea Falco for his help with the statistical analyses. Work partly supported by Associazione Italiana Ricerca sul Cancro (AIRC), Special 5×1000 Program Metastases (21198), Milan (Italy) to Robin Foà and Progetti di Rilevante Interesse Nazionale (PRIN) Italia, 2017PPSX4 project to Massimiliano Bonifacio and Sabina Chiaretti. Michelina Dargenio, Massimiliano Bonifacio, Sabina Chiaretti, Giovanni Pizzolo and Robin Foà designed the study, analysed data and drafted the manuscript. Michelina Dargenio, Massimiliano Bonifacio, Sabina Chiaretti, Antonella Vitale, Nicola Stefano Fracchiolla, Cristina Papayannidis, Fabio Giglio, Prassede Salutari, Ernesta Audisio, Barbara Scappini, Patrizia Zappasodi, Marzia Defina, Fabio Forghieri, Anna Maria Scattolin, Elisabetta Todisco, Monia Lunghi, Fabio Guolo, Maria Ilaria Del Principe, Mario Annunziata, Davide Lazzarotto, Michele Cedrone, Crescenza Pasciolla, Annalisa Imovilli, Ilaria Tanasi, Silvia Trappolini, Marco Cerrano, Roberta La Starza, Mauro Krampera and Nicola Di Renzo contributed to patient recruitment and data collection. Michelina Dargenio, Massimiliano Bonifacio, Sabina Chiaretti, Anna Candoni, Giovanni Pizzolo, Felicetto Ferrara and Robin Foà acted as coordinators of the Campus ALL network. All authors gave final approval to the manuscript and agreed to be accountable for the accuracy and integrity of the work.

CONFLICT OF INTEREST

No conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Michelina Dargenio https://orcid.org/0000-0003-0924-4629
Massimiliano Bonifacio https://orcid.org/0000-0003-0716-1686
Sabina Chiaretti https://orcid.org/0000-0001-8499-4492
Fabio Giglio https://orcid.org/0000-0003-4755-9533
Fabio Guolo https://orcid.org/0000-0003-3166-6078
Marco Cerrano https://orcid.org/0000-0003-1666-3100

REFERENCES

1. Hunger SP, Mullighan CG. Acute lymphoblastic leukemia in children. N Engl J Med. 2015;373(16):1541–52.
2. Siegel SE, Stock W, Johnson RH, Advani A, Muffly L, Douer D, et al. Pediatric-inspired treatment regimens for adolescents and young adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: a review. JAMA Oncol. 2018;4(5):725–34.
3. Boissel N, Baruchel A. Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children? Blood. 2018;132(4):351–61.
4. Huguet F, Leguay T, Raffoux E, Thomas X, Beldjord K, Chevallier ED, et al. Pediatric inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol. 2009;27(6):911–8.
5. Huguet F, Chevret S, Leguay T, Thomas X, Boissel N, Escoffre-Barbe M, et al. Intensified therapy of acute lymphoblastic leukemia in adults: report of the randomized GRAALL-2005 clinical trial. J Clin Oncol. 2018;36(24):2514–23.
6. Lazarus HM, Richards SM, Chopra R, Litzow MR, Burnett AK, Wiernik PH, et al. Central nervous system involvement in adult acute lymphoblastic leukemia at diagnosis: results from the international ALL trial MRC UKALL XII/ECOG E2993. Blood. 2006;108:465–72.
7. Gokbuget N, Hoelzer D. Meningeosis leukaemica in adult acute lymphoblastic leukaemia. J Neurooncol. 1998;38(2–3):167–80.
8. Orvain C, Chantepie S, Thomas X, Escoffre-Barbe M, Huguet F, Desbrosses Y, et al. Impact of Central Nervous System involvement in adult patients with acute lymphoblastic leukemia Treated in a Pediatrics-Inspired Protocol – a Graall Study. Blood. 2021;138(s1): abstract 612; 215–17.
9. Del Principe MI, Buzzatti E, Piciocchi A, Forghieri F, Bonifacio M, Lessi F, et al. Clinical significance of occult central nervous system disease in adult acute lymphoblastic leukemia. A multicenter report from the campus ALL network. Haematologica. 2021;106(1):39–45.
10. Cortes J, O'Brien SM, Pierce S, Keating MJ, Freireich EJ, Kantarjian HM. The value of high dose systemic chemotherapy and intrathecal therapy for central nervous system prophylaxis in different risk groups of adult acute lymphoblastic leukemia. Blood. 1995;86(6):2091–7.
11. Kantarjian HM, O'Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen in adult acute lymphocytic leukemia. J Clin Oncol. 2000;18(3):547–61.
12. Surapaneni UR, Cortes JE, Thomas D, O'Brien S, Giles FJ, Koller C, et al. Central nervous system relapse in adults with acute lymphoblastic leukemia. Cancer. 2002;94(3):773–9.
13. Reman O, Pigneux A, Huguet F, Vey N, Delannoy A, Fegueux N, et al. Central nervous system involvement in adult lymphoblastic leukemia at diagnosis and/or at first relapse: results from the GET-LALA group. Leuk Res. 2008;32(11):1741–50.
14. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007;109(3):944–50.
15. Sancho JM, Ribera JM, Oriol A, Hernandez-Rivas JM, Rivas C, Bethencourt C, et al. Programa Para el Estudio y Tratamiento de Hemopatias Malignas group. Central nervous system recurrence in adult patients with acute lymphoblastic leukemia: frequency and prognosis in 467 patients without cranial irradiation for prophylaxis. Cancer. 2006;106(12):2540–5.
16. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in pediatric leukemia. Lancet Oncol. 2008;9(3):257–68.
17. Larson RA. Managing CNS disease in adults with acute lymphoblastic leukemia. Leuk Lymphoma. 2018;59(1):3–13.
18. Aldoss I, Al Malki MM, Stiller T, Cao T, Sanchez JF, Palmer J, et al. Implications and management of central nervous system involvement before allogeneic hematopoietic cell transplantation in acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2016;22(3):575–8.
19. Hamdi A, Mawad R, Bassett R, di Stasi A, Ferro R, Afrough A, et al. Central nervous system relapse in adults with acute lymphoblastic leukemia after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2014;20(11):1767–71.
20. Bassan R, Pavoni C, Intermesoli T, Spinelli O, Tosi M, Audisio E, et al. Updated risk-oriented strategy for acute lymphoblastic leukemia in adult patients18-65 years: NILG ALL 10/07.Blood. Cancer J. 2020;10:119–32.
21. Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grümayer R, Möricke A, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL2000 study. Blood. 2010;115(16):3206–14.
22. Testi AM, Canichella M, Vitale A, Piciocchi A, Guarini A, Della Starza I, et al. Adolelescent and young adult acute lymphoblastic leukemia. Final results of the phase II pediatric-like GIMEMA LAL-1308. Am J Hematol. 2021;96:292–301.
23. Bassan R, Chiaretti S, Della Starza I, Spinelli O, Santoro A, Elia L, et al. National Pegaspargase modified risk oriented program for Philadelphia negative adult acute lymphoblastic leukemia/lymphoblastic lymphoma (Ph– ALL/LL). GIMEMA LAL 1913 final results. HemaSphere. 2022;(6): abstract 113; 14–15.
24. Faderl S, Kantarjian HM, Talpaz M, Estrov Z. Clinical significance of cytogenetic abnormalities in adult acute lymphoblastic leukemia. Blood. 1998;91(11):3995–4019.
25. Moorman AV, Harrison CJ, Buck GA, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/eastern cooperative oncology group (ECOG) al. Blood. 2007;109(8):3189–97.
26. Charrin C, Thomas X, Ffrench M, Le QH, Andrieux J, Mozziconacci MJ, et al. A report from the LALA-94 and LALA-SA groups on hypodiploidy with 30 to 39 chromosomes and near triploidy:2 possible expressions of a sole entity conferring poor prognosis in adult acute lymphoblastic leukemia (ALL). Blood. 2004;104(8):2444–51.
27. Thomas X, Le QH. Central nervous system involvement in adult acute lymphoblastic leukemia. Hematology. 2008;13(5):293–302.
28. Mahmoud HH, Rivera GK, Hancock ML, Krance RA, Kun LE, Behm FG, et al. Low leukocyte counts with blast cells in cerebrospinal fluid of children with newly diagnosed acute lymphoblastic leukemia. N Engl JMed. 1993;329(5):314–9.
29. Quijano S, Lopez A, Sancho JM, Panizo C, Debén G, Castilla C, et al. Spanish Group for the Study of CNS disease in NHL. Identification of leptomeningeal disease in aggressive B-cell non Hogkin's lymphoma: improved sensitivity of flow cytometry. J Clin Oncol. 2009;27(9):1462–9.
30. Chiaretti S, Messina M, Grammatico S, Piciocchi A, Fedullo AL, Di Giacomo F, et al. Rapid identification of BCR/ABL1-like acute

lymphoblastic leukemia patients using a predictive statistical model based on quantitative real time-polymerase chain reaction: clinical, prognostic and therapeutic implications. Br J Haematol. 2018 Jun;181(5):642–52.
31. Gökbuget N, Dombret H, Ribera JM, Fielding AK, Advani A, Bassan R, et al. International reference analysis of outcomes in adults with B-precursor Ph-negative relapsed/refractory acute lymphoblastic leukemia. Haematologica. 2016;101(12):1524–33.
32. Cancela CS, Murao M, Viana MB, de Oliveira BM. Incidence and risk factors for central nervous system relapse in children and adolescents with acute lymphoblastic leukemia. Rev Bras Hematol Hemoter. 2012;34(6):436–41.
33. Chiaretti S, Messina M, Della Starza I, Piciocchi A, Cafforio L, Cavalli M, et al. Philadelphia-like acute lymphoblastic leukemia is associated with minimal residual disease persistence and poor outcome. First report of the minimal residual disease-oriented GIMEMA LAL1913. Haematologica. 2021;106(6):1559–68.
34. Roberts KG, Gu Z, Payne-Turner D, McCastlain K, Harvey RC, Chen IM, et al. High frequency and poor outcome of Philadelphia chromosome–like acute lymphoblastic leukemia in adults. J Clin Oncol. 2017;35(4):394–401.
35. Mullighan CG. Molecular genetics of B-precursor acute lymphoblastic leukemia. The J Clin Invest. 2012;122(10):3407–15.
36. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014;371(11):1005–15.
37. Roberts KG, Janke LJ, Zhao Y, Seth A, Ma J, Finkelstein D, et al. ETV6-NTRK3 induces aggressive acute lymphoblastic leukemia highly sensitive to selective TRK inhibition. Blood. 2018;132(8):861–5.
38. Nguyen K, Devidas M, Cheng SC, La M, Raetz EA, Carroll WL, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's oncology group study. Leukemia. 2008;22(12):2142–50.
39. Foà R, Bassan R, Vitale A, Elia L, Piciocchi A, Puzzolo MC, et al. Dasatinib-blinatumomab for Ph-positive acute lymphoblastic leukemia in adults. N Engl J Med. 2020;383(17):1613–23.
40. Chiaretti S, Bassan R, Vitale A, Elia L, Messina M, Piciocchi A, et al. Updated results of the GIMEMA LAL2116, D-ALBA Trial, for newly diagnosed adults with PH+ ALL. Abstract 112. Presented at the 26th virtual Congress of European Hematology Association, June 9–17, 2021.
41. de Graaf MT, de Jongste AH, Kraan J, Boonstra JG, Sillevis Smitt PA, Gratama JW. Flow cytometric characterization of cerebrospinal fluid cells. Cytometry B Clin Cytom. 2011;80(5):271–81.
42. Zeiser R, Burger JA, Bley TA, Windfuhr-Blum M, Schulte-Mönting J, Behringer DM. Clinical follow-up indicates differential accuracy of magnetic resonance imaging and immunocytology of the cerebral spinal fluid for the diagnosis of neoplastic meningitis-a single Centre experience. Br J Haematol. 2004;124(6):762–8.
43. Dinndorf PA, Gootenberg J, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: pegaspargase (Oncospar) for the first-line treatment of children with acute lymphoblastic leukemia (ALL). Oncologist. 2007;12(8):991–8.
44. Liu C, Huang B, Wu R, Chen J, Tang Y, Hu W, et al. Adequate asparaginase is important to prevent central nervous system and testicular relapse of pediatric Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia. Int J Cancer. 2021;149(1):158–68.
45. Jeha S, Pei D, Choi J, Cheng C, Sandlund JT, Coustan-Smith E, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total therapy study 16. J Clin Oncol. 2019;37(35):3377–91.
46. Brown PA, Ji L, Xu X, Devidas M, Hogan LE, Borowitz MJ, et al. A randomized phase 3 trial of blinatumomab vs. chemotherapy as post-reinduction therapy in low risk (LR) first relapse of B-acute lymphoblastic leukemia (B-ALL) in children and adolescents/young adults (AYAs): a report from Children's oncology group study AALL1331. Blood. 2021;138(s1): abstract 614; 363–65.
47. Leahy AB, Newman H, Li Y, Liu H, Myers R, Di Nofia A, et al. CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: a post-hoc analysis of pooled data from five clinical trials. Lancet Haematol. 2021;8(10):e711–22.
48. Ding YY, Stern JW, Jubelirer TF, Wertheim GB, Lin F, Chang F, et al. Clinical efficacy of ruxolitinib and chemotherapy in a child with Philadelphia chromosome-like acute lymphoblastic leukemia with GOLGA5-JAK2 fusion and induction failure. Haematologica. 2018;103(9):e427–31.
49. Chantepie SP, Mohty M, Tabrizi R, Robin M, Deconinck E, Buzyn A, et al. Treatment of adult ALL with central nervous system involvement at diagnosis using autologous and allogeneic transplantation: a study from the Societe´ Francaise de Greffe de Moelle et de Therapie Cellulaire. Bone Marrow Transplant. 2013;48:684–90.
50. Ge L, Ye F, Mao X, Chen J, Sun A, Zhu X, et al. Extramedullary relapse of acute leukemia after allogeneic hematopoietic stem cell transplantation: different characteristics between acute myelogenous leukemia and acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2014;20(7):1040–7.
51. Sapienza MR, Benvenuto G, Ferracin M, Mazzara S, Fuligni F, Tripodo C, et al. Newly- discovered neural features expand the pathobiological knowledge of blastic plasmacytoid dendritic cell neoplasm. Cancer. 2021;13(18):4680–94.

How to cite this article: Dargenio M, Bonifacio M, Chiaretti S, Vitale A, Fracchiolla NS, Papayannidis C, et al. Incidence, treatment and outcome of central nervous system relapse in adult acute lymphoblastic leukaemia patients treated front-line with paediatric-inspired regimens. A retrospective multicentre Campus ALL study. Br J Haematol. 2023;200(4):440–450. https://doi.org/10.1111/bjh.18537