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Short title: CNS-3 status remains an independent adverse prognosis factor in children with ALL treated without cranial irradiation

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Conflicts of interest: none

Abstract

Aim: To evaluate the prognostic significance of initial central nervous system (CNS) involvement of in children with acute lymphoblastic leukemia (ALL) enrolled in the EORTC 58951 trial.

Patients and Methods: From 1998 to 2008, 1930 ALL patients were included in the randomized EORTC 58951 trial. Overall treatment intensity was adjusted according to known prognostic factors including the level of minimal residual disease after induction treatment. CNS-directed therapy comprised four to 11 courses of i.v. methotrexate (5 g/m^2), and 10 to 19 intrathecal chemotherapy injections, depending on risk group and CNS status. Cranial irradiation was omitted for all patients.

Results: The overall 8-year event-free survival (EFS) and overall survival (OS) rates were 81.3% and 88.1%, respectively. In the CNS-1, TPL+, CNS-2, and CNS-3 groups, the 8-year EFS rates were 82.1%, 77.1%, 78.3%, and 57.4%, respectively. Multivariable analysis indicated that initial CNS-3 status, but not CNS-2 or TLP+, was an independent adverse predictor of outcome. The 8-year incidence of isolated CNS-relapse was 1.7% and of isolated or combined CNS relapse it was 3.7%. NCI high-risk group, male sex, CNS-2 and CNS-3 status were independent predictors for a higher incidence of any CNS relapse.

Conclusions: CNS-3 status remains associated with poor prognosis and requires intensification of both systemic and CNS-directed therapy.

Keywords: children, acute lymphoblastic leukemia, central nervous system

This trial was registered at https://clinicaltrials.gov/under NCT00003728

1. Introduction

Central nervous system (CNS)-directed therapy is an essential component of acute lymphoblastic leukemia (ALL) treatment, including cranial irradiation (XRT), intrathecal (IT) therapy, effective systemic chemotherapy, or a combination of these modalities. The use of XRT has become contentious because of its late adverse effects [1]. We have shown previously that cranial XRT failed to provide any benefit to medium- and high-risk patients having received high-dose methotrexate (HD MTX) [2].

EORTC 58881 was the first EORTC trial in which XRT was omitted for all patients including those with initial overt CNS leukemia involvement. Good outcomes in CNS-3 patients suggested that a strategy without XRT based on intensification of systemic therapy was valuable even in patients with overt leukemia at diagnosis [3]. The subsequent EORTC 58951 trial, which omitted XRT in all patients as well, included three randomized questions: (a) the value of dexamethasone (6 mg/m^2/day) versus prednisone (60 mg/m^2/day) in induction [4]; (b) the value of an increased number of administrations of L-asparaginase throughout consolidation and late intensification for patients without very high risk [5]; (c) the value of vincristine-corticosteroid pulses added to continuation therapy for average-risk patients [6]**.**

The aim of this study was to evaluate the prognostic importance of CNS status of children recruited in the EORTC 58951 trial.

2. Patients and methods

2.1 Patients

From December 1998 to August 2008, 1947 children (< 18 years old) with newly diagnosed ALL were prospectively enrolled in the EORTC 58951 trial. Minimal residual disease (MRD) monitoring was based on quantitative detection of leukemic clone-specific T-cell-receptor/immunoglobulin gene rearrangements [4-6]. Patients were assigned to different risk groups: very low risk (VLR), average risk low (AR1), average risk high (AR2), and very high risk (VHR) [4,5]. VLR was defined as B-lineage ALL with hyperdiploid karyotype (>50 chromosomes) or DNA index >1.16 and < 1.50, and with white blood cell (WBC) counts < 10×10^9/L, and absence of CNS and gonadal involvement, and absence of VHR criteria. VHR criteria consisted of blast count in peripheral blood ≥ 1×10^9/L at completion of the prephase (day 8), presence of

t(9;22), of t(4;11) or another MLL rearrangement, near-haploidy (≤ 34 chromosomes), acute undifferentiated leukemia, failure to achieve complete remission (CR) or MRD ≥ 10^{-2} at completion of induction. AR patients were children without VLR or VHR characteristics, subdivided into AR1 (B-cell lineage ALL patients with WBC counts below 100×10^9/L without CNS involvement) or AR2 (B-cell lineage ALL patients with WBC count ≥100×10^9/L or T-cell lineage ALL patients) groups [6].

CNS status was based on cytomorphology and defined as CNS-1 (no blast cells in a sample of cerebrospinal fluid), CNS-2 (< 5 WBC/mm^3 with blasts in a sample with <10 erythrocytes/mm^3), CNS-3 (≥ 5 WBC/mm^3 with blast cells in a sample with <10 erythrocytes/mm^3 and/or cranial nerve palsies and/or other neurological abnormality attributed to leukemic involvement), or traumatic lumbar puncture with blast cells (TLP+) (>10 erythrocytes/mm^3 with blasts cells). The CNS+ group included all patients with CNS involvement at diagnosis: TLP+, CNS-2, and CNS-3. All patients with CNS-3 status, or any CNS involvement at the first lumbar puncture examination performed 3 days after the initial one, and without any VHR criterion, were included in the AR2 group.

2.2. Treatment programs

The treatment regimen, adapted from the BFM protocol, has been previously described in detail (**Figure 1**) [4-6]. The treatment for the VLR and AR groups was based on induction-consolidation, CNS-directed therapy with HD MTX and late intensification, followed by a continuation therapy of 74-week duration. The VHR patients received an induction-reinforced consolidation (IB')-VANDA. The VHR patients who met the eligibility criteria for hematopoietic stem cell transplantation (HSCT) and who had an HLA identical donor underwent HSCT [4-6]. All other VHR patients continued chemotherapy with interval therapy followed by two sequences of R1, R2, and R3 courses and by continuation therapy for a total treatment duration of 2 years.

2.3. Therapy directed to the CNS

IT methotrexate was instilled immediately after a diagnostic lumbar puncture and triple (methotrexate, cytarabine, hydrocortisone) IT chemotherapy was used in all subsequent treatments, except for VLR patients (IT methotrexate). CNS-3 patients received additional CNS-directed therapy: IT injections every fourth day during prephase and induction until disappearance of leukemic blasts from the CSF, two additional IT injections

during induction and two during consolidation. CNS-2 and TLP+ patients were treated in the same way as CNS-3 patients if leukemic blasts were still present in the CSF at day 4 (second IT injection). Depending on the presenting patients' characteristics and the CNS status, patients received 10 to 19 IT treatments. Courses of HD MTX (5 g/m^2 over 24 h) were given to all patients: four times for VLR and AR1 patients, and 11 or 10 times for AR2 and VHR patients, respectively. No XRT was used, neither to the CNS nor to the testes.

2.4. Statistical analysis

The Kaplan–Meier technique was used to estimate survival-type distributions (EFS, DFS, and OS) and the standard errors (SE) of the estimates were obtained via the Greenwood formula [7]. The estimates of the incidence of isolated CNS relapse and of isolated or combined CNS relapse were obtained using the competing risk methods, and they were compared using the Gray test. In multivariate analysis, the following variables were considered: initial WBC (< 25, 25–99, $\geq$ 100×10^9/L), immunophenotyping (T- vs. B-lineage ALL), NCI risk group (high vs. standard risk), initial VHR features (presence vs. absence), type of corticosteroids (dexamethasone vs. prednisone), CNS status. For DFS, the MRD level ($\geq 10^{-2}$ vs. $<10^{-2}$) at the end of induction was considered as covariate in the respective models. The statistical software SAS 9.4 was used for the analyses.

3. Results

A total of 1930 patients were evaluable for initial CNS status evaluation. There were 1791 (92.7%) CNS-1, 27 (1.4%) TLP+ patients, 71 (3.7%) CNS-2 and 41 (2.1%) CNS-3 patients (**Table 1**). CNS+ patients had more unfavorable features than CNS-1 patients, i.e., WBC counts above 100×10^9/L, NCI high risk, VHR features and T-lineage (**Table 1**). Overall, 19 (70%) of the TLP+ patients and 37 (52 %) of the CNS-2 patients were treated in the same way as CNS-3 patients because of the persistence of at least one leukemic blast in the first control lumbar puncture.

Among 1930 patients, 23 did not reach CR after induction or consolidation. Out of the remaining 1907 patients, after a median follow-up duration of 6.9 years, 1587 were still alive in continuous CR, 285 relapsed, and 35 died in CR. The overall 8-year EFS and OS rates were 81.3% and 88.1%, respectively. In the CNS-1, TLP+, CNS-2, and CNS-3 groups, the 8-year EFS (SE%) rates were 82.1% (1.0%), 77.1% (8.2%), 78.3% (5.2%), and

57.4% (7.9%), respectively (**Figure 2**), and the 8-year OS rates (SE%) were 88.8% (0.8%), 83.8% (7.5%), 86.6% (4.6%), and 62.7% (8.2%), respectively (**Figure 3**). For both endpoints, the difference between the outcomes according to the CNS status was mainly due to the worse outcome of CNS-3 patients (**Table 2**).

Cox multivariate analysis indicated that presence of initial VHR features, NCI high-risk characteristics, CNS-3 status, and male sex were independently, related to shorter EFS and OS, whereas CNS-2 or TLP+ status had the same relative prognosis as CNS-1 status (**Table 2**). These results were not impacted by the treatment allocation group (dexamethasone vs. prednisone; data not shown).

For 1907 patients who reached CR, the 8-year DFS rate was 82.3%. As for EFS and OS, initial CNS status impacted the DFS significantly: the 8-year DFS rate (SE%) was 83.1% (0.9%) for CNS-1 patients, 80.0% (8.0%) for the TLP + group, 78.3% (5.2%) for CNS-2 patients, and 60.3% (8.1%) for CNS-3 patients (Table 2). As for EFS and OS endpoints, multivariate analyses also revealed that CNS status was still of prognostic importance, even by adjusting for other factors (e.g., initial VHR features). CNS-3 patients, and patients with a high level of MRD ($\geq 10^{-2}$) at the end of induction, had a higher risk of relapse or death than those with CNS-1 status and a lower level of MRD, respectively (**Table 2**).

Among 285 patients who relapsed, 217 had a non-CNS relapse, 33 had an isolated relapse, and 35 had a combined CNS relapse. The 8-year overall isolated CNS relapse cumulative incidence was 1.7% overall, and according to CNS status it was 1.5% in the CNS-1 group, 0% in TLP+, 2.8% in CNS-2, and 12.8% in the CNS-3 group (**Table 3**). In CNS+ patients, this 8-year incidence was 5.2%, which was significantly higher (p=0.0016) than the 1.5% observed in CNS-1 patients.

The 8-year cumulative incidence for any (isolated and combined) CNS relapse was 3.7% overall, and according to CNS status it was: 3.3% in the CNS-1, 3.8% in the TLP+, 9.2% in the CNS-2, and 12.8% in the CNS-3 group (**Table 3**). In CNS+ patients, this 8-year incidence was 9.2%, being significantly higher (p<0.01) than the 3.3% reported for CNS-1 patients. Fine–Gray multivariate analysis indicated that CNS-2 status (vs. CNS-1: HR=2.46, p=0.04), CNS-3 status (vs. CNS-1: HR=2.89, p=0.03), male sex (vs. female: HR=2.26, p=0.003), NCI high-risk group (vs. standard risk: HR=2.02, p=0.008), EORTC VHR (vs. VLR: HR=2.91, p=0.10), and high MRD at the end of induction (vs. $< 10^{-2}$: HR=1.99, p=0.10) were independently associated with a higher incidence of isolated or combined CNS relapse.

4. Discussion

The 8-year EFS and OS rates in the EORTC 58951 study were 81.3% and 88.1%, respectively, which is similar to the results of major contemporary studies reported to date [8-15]. As compared with the results of the EORTC 58881 study, the EFS and OS have improved, and both CNS and non-CNS relapses have decreased in all CNS groups, except for CNS-3 (**Table 3 and Table S1**) [3]. The poorer outcome of CNS-3 patients in the EORTC 58951 study versus the previous 58881 study (8-year EFS rate: 57.4% vs. 68.3%, 8-year OS rate: 62.7% vs. 67.4%) was associated with a higher 8-year cumulative incidence of non-CNS relapses (21.7% vs. 11.6%) [3]. We have no explanation for this difference since the intensity of systemic chemotherapy was comparable in the two protocols. However, our results from the CNS-3 group are in the same range as reported in most major clinical trials including or not including CNS XRT [8-15]. The complete omission of XRT in CNS-3 patients has been recently justified by the NOPHO group, indicating that XRT did not improve OS [16]. Moreover, patients with isolated CNS relapse who have not received prophylactic irradiation could be cured, as suggested by Pui et al. [11]. Interestingly, the small difference between the cumulative incidence of isolated CNS relapses and isolated plus combined CNS relapses, observed in both EORTC studies (**Table 3**), confirms, in agreement with a previous meta-analysis, that the intensity of systemic therapy, particularly HD MTX courses, predominantly affects the marrow rather than the CNS compartment [14].

CNS2 status was not associated with an inferior outcome in the EORTC 58951 study. The 8-year EFS rate of 78.3% for CNS-2 patients was higher than the one reported in the DCOG ALL-8 study (70.3%) and was similar to that of the BFM 95 trial (80%) [8,9]. The better results reported by the St. Jude Children's Hospital Total Therapy XV Protocol (86.2%), or the Dana Farber Protocol 00-01 (84%), the latter applying cranial irradiation of 18 Gy, could be partly related to the different proportion of CNS-2 patients. In these two studies, 20.4% and 12% of the patients, respectively, had a CNS-2 status, which is much higher than the 2.1% in the EORTC 58951 study [10,12]. We therefore speculate that some CNS-2 patients with only very few blasts in the CSF, i.e., those with a "minimal meningeal leukemia," were classified as having CNS-1 status in our study. This bias ("stage migration") could explain, in part, the discrepancy in outcome. However, the higher incidence of any CNS relapse in CNS-2 patients warrants intensification of CNS-directed therapy in this group.

Measurement of MRD is widely applied in current childhood ALL studies [17,18]. The AIEOP-BFM ALL 2000 study recently concluded that MRD response in ALL detected by sensitive PCR techniques is highly predictive of relapse, thus markedly reducing the importance of conventional prognostic factors [19]. Nevertheless, in our study, CNS-3 status retained independent prognostic value even in multivariate analysis including MRD < 10^{-2} at the end of induction. Of note, recent protocols now stratify MRD at end-of-induction with a more sensitive threshold (10^{-3} or less), and our results need to be confirmed with such levels of MRD. However, the AIEOP-BFM 2000 study suggests that extramedullary relapses, especially isolated relapses, are probably not predicted by bone marrow MRD response, even at a 10^{-4} detection level [20].

5. Conclusion

Adjusting for other factors, including MRD study, CNS-3 remains associated with poor prognosis and needs intensification of systemic and CNS-directed therapy. The EORTC group is currently planning a retrospective study to confirm that patients with isolated CNS relapse who have not received prophylactic irradiation can be cured with second-line treatment.

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References

1. Pui CH, Howard SC. Current management and challenges of malignant disease in the CNS in paediatric leukaemia. Lancet Oncol 2008;9:257-68.

2. Piette C, Suciu S, Bertrand Y, et al. Long-term outcome evaluation of medium/high risk acute lymphoblastic leukaemia children treated with or without cranial radiotherapy in the EORTC 58832 randomized study. Br J Haematol 2020;189:351-62.

3. Sirvent N, Suciu S, Rialland X, et al. Prognostic significance of the initial cerebro-spinal fluid (CSF) involvement of children with acute lymphoblastic leukaemia (ALL) treated without cranial irradiation: results of European Organization for Research and Treatment of Cancer (EORTC) Children Leukemia Group study 58881. Eur J Cancer 2011;2:239-47.

4. Domenech C, Suciu S, De Moerloose B, et al. Dexamethasone (6 mg/m2/day) and prednisolone (60 mg/m2/day) were equally effective as induction therapy for childhood acute lymphoblastic leukemia in the EORTC CLG 58951 randomized trial. Haematologica 2014;7:1220-7.

5. Mondelaers V, Suciu S, De Moerloose B, et al. Prolonged versus standard native E. coli asparaginase therapy in childhood acute lymphoblastic leukemia and non-Hodgkin lymphoma: final results of the EORTC-CLG randomized phase III trial 58951. Haematologica 2017;102:1727-38.

6. De Moerloose B, Suciu S, Bertrand Y, et al. Improved outcome with pulses of vincristine and corticosteroids in continuation therapy of children with average risk acute lymphoblastic leukemia (ALL) and lymphoblastic non-Hodgkin lymphoma (NHL): report of the EORTC randomized phase 3 trial 58951. Blood 2010;1:36-44.

7. Kalbfleisch JD and Prentice RL. The Survival Analysis of Failure Time Data. Second Edition. New-Jersey, USA: Wiley Inter-Science, 2002, 462p. (Wiley Series in Probabilities and Statistics)

8. te Loo DM, Kamps WA, van der Boes-van den Berg A, et al. Prognostic significance of blasts in the cerebrospinal fluid without pleiocytosis or a traumatic lumbar puncture in children with acute lymphoblastic leukemia: experience of the Dutch Childhood Oncology Group. J Clin Oncol 2006;24:2332-6.

9. Burger B, Zimmerman M, Mann G, et al. Diagnostic fluid examination in children with acute lymphoblastic leukemia: significance of low leucocyte counts with blasts or traumatic lumbar puncture. J Clin Oncol 2003;21:184-8.

10. Pui CH, Sandlund JT, Pei D, et al. Improved outcome for children with acute lymphoblastic leukemia: Results of Total Therapy Study XIIIB at St Jude Children's Research Hospital. Blood 2004;104:2690-6.

11. Pui CH, Campana D, Pai D, et al. Treating childhood acute lymphoblastic leukaemia without cranial irradiation. N Engl J Med 2009;360:2730-41.

12. Vrooman LM, Stevenson KE, Supko JG, et al. Postinduction Dexamethasone and Individualized Dosing of Escherichia Coli L-Asparaginase Each Improve Outcome of Children and Adolescents With Newly Diagnosed Acute Lymphoblastic Leukemia: Results from a Randomized Study-Dana Farber Cancer Institute ALL Consortium Protocol 00-01. J Clin Oncol 2013;31:1202-10.

13. Veerman A, Kamps W, van den Berg H, et al. Dexamethasone-based therapy for childhood acute lymphoblastic leukaemia: results of the prospective Dutch Childhood Oncology Group (DCOG) protocol ALL-9 (1997-2004). Lancet Oncol 2009;109:957-66.

14. Clarke M, Gaynon P, Hann I, et al. CNS-directed therapy for childhood acute lymphoblastic leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials. J Clin Oncol 2003;21:1798-809

15. Winick N, Devidas M, Chen S, et al. Impact of initial CSF findings on outcome amog patients with national cancer institute standard- and high-risk B-cell acute lymphoblastic leukemia: a report from the children's oncology group. J Clin Oncol 2017; 35:2527-34.

16. Taskinen M, Oskarsson T, Levinsen M, et al. The effect of central nervous system involvement and irradiation in childhood acute lymphoblastic leukemia lessons from the NOPHOALL-92 and ALL-2000 protocols. Pediatr Blood Cancer 2017;64:242–9.

17. Vora A, Goulden N, Mitchell C, et al. Augmented post-remission therapy for a minimal residual disease-defined high-risk subgroup of children and young people with clinical standard-risk and intermediate-risk acute lymphoblastic leukaemia (UKALL 2003): a randomised controlled trial. Lancet Oncol 2014;15:809-18.

18. Stow P, Key L, Chen X, et al. Clinical significance of low levels of minimal residual disease at the end of remission induction therapy in childhood acute lymphoblastic leukemia. Blood 2010;10:4657-63.

19. Conter V, Bartram CR, Valsecchi MG, et al. Childhood high-risk acute lymphoblastic leukemia in first remission: results after chemotherapy or transplant from the AIEOP ALL 2000 study. Blood 2014;6:1470-8.

20. Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood 2011;25:2077-84.

Figures:

Figure 1: General design of the EORTC-CLG 58951 trial

R1: all patients, before the prephase or the phase IA, according to the decision of the investigating center.

	arm 1: PRED: Prednisolone arm 2: DEXA: Dexamethasone
R2: all patients except VHR	arm S: L-Asparaginase short (Total 12 infusion) arm L: L-Asparaginase long (Total 24 infusions)
R3: AR patients	arm MA: no pulses arm MB: pulses VCR + corticosteroid

EORTC: European Organisation for Research and Treatment of Cancer; VHR: very high risk; AR: average risk

Figure 2: Event-free survival according to CNS status

O: observed number of events; N: number of patients randomized.

CNS: Central nervous system; TLP+: traumatic lumbar puncture with blast cells

Figure 3: Overall survival according to CNS status
O: observed number of events; N: number of patients randomized
CNS: Central nervous system; TLP+: traumatic lumbar puncture with blast cells

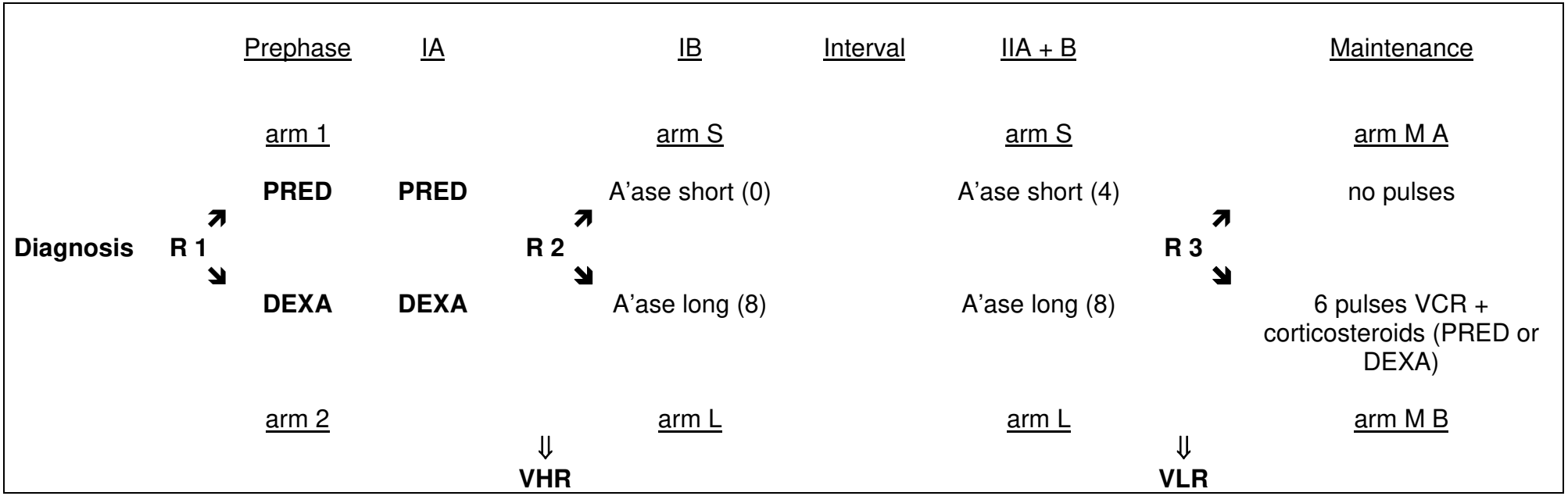

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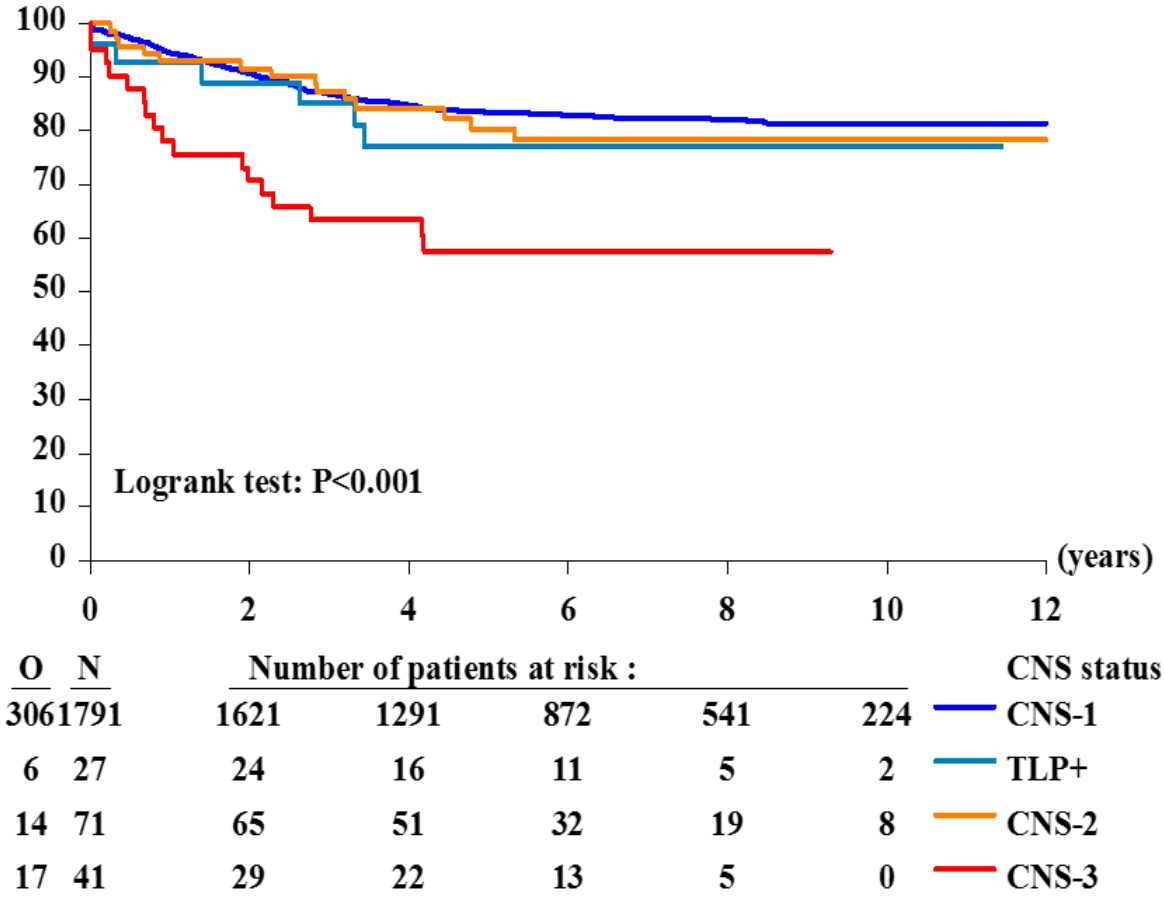
Figure 1 : General design of the EORTC-CLG trial 58951



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O: observed number of events; N: number of patients randomized.

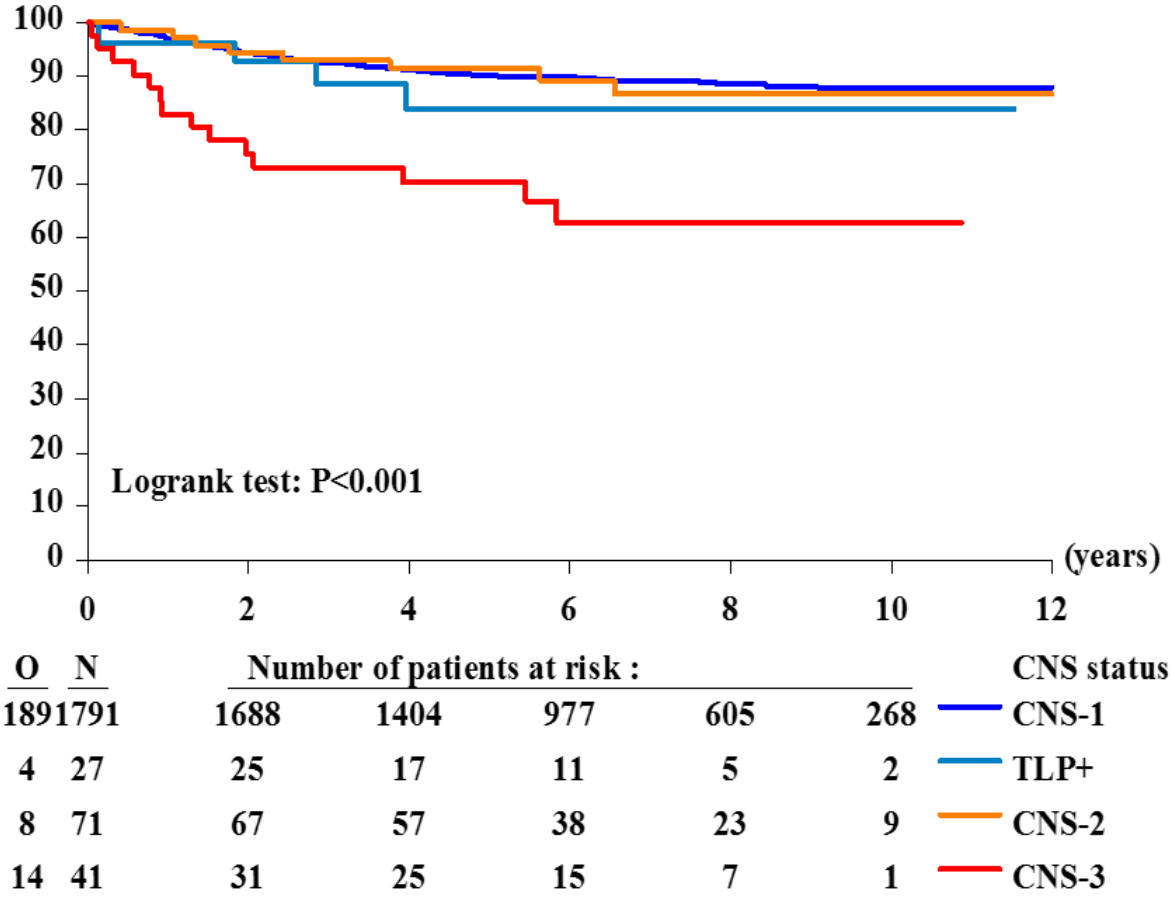

Figure 3: Overall Survival according to CNS-status
O: observed number of events; N: number of patients randomized.

Table 1: Patient characteristics, overall and according to central nervous system status

	All patients		CNS-1		TLP+		CNS-2		CNS-3	
Characteristics	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
All	1930	100	1791	100	27	100	71	100	41	100
Sex										
Male	1060	55	986	55	12	44	37	52	25	61
Female	870	45	805	45	15	56	34	48	16	39
Age, years										
< 1	5	<1	4	<1	0	0	0	0	1	2
1-<10	1452	75	1348	75	15	55	62	87	27	66
≥10	473	25	439	25	12	46	9	13	13	32
Immunology										
B-lineage	1641	85	1544	86	19	70	57	80	21	51
T-lineage	288	15	246	14	8	30	14	20	20	49
AUL	1		1							
WBC, $\times 10^9$/L										
< 100	1728	90	1627	91	17	63	53	75	32	78
≥ 100	202	10	164	9	10	37	18	25	9	22
EORTC Risk group										
Very Low Risk	249	13	248	14	0	0	1	1	0	0
Average Risk 1	1119	58	1090	61	5	18	23	32	1	2
Average Risk 2	294	15	211	12	18	67	35	49	30	73
Very High Risk	268	14	242	13	4	15	12	17	10	24
Blast count after prephase (/mm^3)										
< 1,000	1731	90	1612	90	25	93	63	89	31	76
≥ 1,000	199	10	179	10	2	7	8	11	10	24
NCI Risk group										
Standard-risk	1177	61	1115	62	8	30	39	55	15	37
High-risk	753	39	676	38	19	70	32	45	26	63
Patients in CR	1907	98.8	1771	98.9	26	96.3	71	100	39	95.1
MRD, *n* and % among patients in CR										
$< 10^{-2}$	1544	80	1430	80	23	86	63	89	28	72
$\geq 10^{-2}$	84	4	76	4	2	7	1	1	5	13
ND/Not evaluable	302	16	285	16	2	7	7	10	8	15

CNS: Central nervous system; TLP+: traumatic lumbar puncture with blast cells; AUL: Acute undifferentiated leukemia; WBC: white blood cell; NCI: National Cancer Institute; CR: complete remission; MRD: minimal residual disease; EORTC: European Organisation for Research and Treatment of Cancer

Table 2: Results of the Cox proportional hazards model regarding EFS, DFS, and OS

	EFS			DFS			OS		
Variable	**HR**	**95% CI (HR)**	***p***	**HR**	**95% CI (HR)**	***p***	**HR**	**95% CI (HR)**	***p***
Univariate analysis			0.0002			<0.0001			<0.0001
TLP+ vs. CNS-1	1.38	(0.62 , 3.10)	0.43	1.24	(0.51 , 3.00)	0.64	1.51	(0.56 , 4.07)	0.42
CNS-2 s vs. CNS-1	1.16	(0.68 , 1.98)	0.59	1.24	(0.73 , 2.12)	0.43	1.07	(0.53 , 2.17)	0.86
CNS-3 vs. CNS-1	3.01	(1.85 , 4.91)	<0.0001	2.89	(1.72 , 4.86)	<0.0001	3.91	(2.27 , 6.73)	<0.0001
Multivariate analysis									
TLP+ vs. CNS-1	1.14	(0.51 , 2.58)	0.74	0.93	(0.38 , 2.26)	0.87	1.15	(0.43 , 3.11)	0.78
CNS-2 s vs. CNS-1	1.06	(0.62 , 1.81)	0.84	1.24	(0.72 , 2.13)	0.43	0.92	(0.45 , 1.86)	0.81
CNS-3 vs. CNS-1	2.27	(1.39 , 3.71)	0.001	1.98	(1.17 , 3.35)	0.01	2.75	(1.59 , 4.75)	0.0003
NCI risk group: High vs. standard risk	1.40	(1.12 , 1.76)	0.004	1.36	(1.08 , 1.73)	0.01	1.76	(1.31 , 2.36)	0.0002
Female vs. Male	0.74	(0.59 , 0.92)	0.007	0.70	(0.56 , 0.88)	0.0025	0.92	(0.70 , 1.21)	0.54
EORTC AR vs. VLR	1.91	(1.19 , 3.07)	0.007	1.79	(2.03 , 3.34)	0.0055	3.17	(1.39 , 7.23)	0.006
EORTC VHR vs. VLR	5.19	(3.12 , 8.61)	< 0.001	4.53	(2.64 , 7.78)	<0.0001	10.82	(4.64 , 25.23)	<0.0001
MRD $\geq 10^{-2}$ vs. $< 10^{-2}$	NA	NA NA	NA	2.86	(2.01 , 4.07)	<0.0001	NA	NA NA	NA
MRD not evaluable vs. $<10^{-2}$	NA	NA NA	NA	1.16	(0.85 , 1.57)	0.35	NA	NA NA	NA

HR, hazard ratio; CI, confidence interval; CNS, Central nervous system; TLP+, traumatic lumbar puncture with blast cells; VLR, very low risk; AR, average risk; VHR, very high risk; MRD, minimal residual disease

Table 3: Outcomes (CR rate, cumulative incidence at 8 years of isolated CNS relapse, of isolated or combined CNS relapse, of death in CR, and 8-year DFS rate), according to initial CNS status in EORTC 58951

At 8 years	CNS-1		TLP+		CNS-2		CNS-3	
	CI (%)	SE (CI)	CI (%)	SE (CI) (%)	CI (%)	SE (CI) (%)	CI (%)	SE (CI) (%)
EORTC 58951								
CR rate*	**98.8**	**0.2**	**96.3**	**2.2**	**100**	**-**	**95.1**	**3.0**
Isolated CNS	1.5	0.3	0	-	2.8	2	12.8	5.3
Any CNS	3.3	0.4	3.8	3.7	9.2	3.6	12.8	5.3
Non-CNS	12.4	0.8	16.1	7.4	11.1	4.0	21.7	6.9
Death in CR	2.1	0.4	0	-	1.4	1.4	5.1	3.5
DFS rate	83	0.9	80	8	78	5.2	60.3	8

*: after induction/consolidation

CNS: Central nervous system; CR: complete remission; TLP+: +: traumatic lumbar puncture with blast cells; CI: cumulative incidence; SE: standard error; DFS: disease-free survival; EORTC: European Organisation for Research and Treatment of Cancer