Outcome of adult T-lymphoblastic lymphoma after acute lymphoblastic leukemia-type treatment: a GOELAMS trial

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ABSTRACT

Background and Objectives

T-lymphoblastic lymphoma is an infrequent disease usually treated as T-acute lymphoblastic leukemia with an induction chemotherapy course and sequential reinduction and maintenance chemotherapy. The T-LBL/ALL-GOELAL02 study evaluated the impact of randomized re-induction chemotherapy against intensified conditioning followed by autologous stem cell transplantation (ASCT), after an induction regimen of the type used for acute lymphoblastic leukemia (ALL).

Design and Methods

Patients with favorable characteristics were randomized to receive chemotherapy or ASCT. Patients with unfavorable characteristics (bone marrow involvement and age over 35 years old or leukocytosis $>30\times10^9$/L or failure to achieve medullar complete remission [CR] after one induction course) received a second induction course and ASCT.

Results

Among 45 patients, the CR rate was 71% after induction and 87% after a second induction course. Within the group of 27 patients with favorable characteristics, ten received ASCT and 17 chemotherapy. Ten patients in the group with unfavorable characteristics received ASCT. The 7-year overall survival and progression-free survival rates were 64 and 65%, respectively. Surprisingly, CR obtained after only two induction courses was associated with improved overall survival (p=0.04). None of the known prognostic factors significantly affected survival.

Interpretation and Conclusions

Randomized maintenance or high-dose therapy (HDT) and ASCT or intensified HDT according to initial presentation gave similar overall and relapse-free survival rates. However, HDT allowed sparing of mediastinal irradiation and shortened treatment duration.

Key words: lymphoblastic lymphoma, autologous bone marrow transplantation, lymphoblastic acute leukemia.

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Lymphoblastic lymphoma (LBL) and acute lymphoblastic leukemia (ALL) have been grouped together into a single entity in the new WHO classification of hematologic malignancies. Even though the cytological and histological features of LBL and ALL are very similar, these two diseases do differ, mostly by the immunophenotypic origin of the clonal proliferation since 80% of LBL blasts have the T-cell phenotype.[1] Therapeutic studies on T-LBL/ALL are scarce[2] and treatments of the type used for non-Hodgkin's lymphoma (NHL) have given disappointing results.[3-5] ALL-type induction regimens have become the standard treatment based on a retrospective analysis of a cohort of 105 children[6] and a smaller, prospective trial in adults.[7] However, the respective benefit of high-dose therapy (HDT) and autologous stem-cell transplantation (ASCT) or maintenance chemotherapy remains to be evaluated. In addition, the therapeutic value of mediastinal radiotherapy is still being discussed.[2,8]

The aim of the T-LBL/ALL GOELAL02 trial was to evaluate, after ALL-type induction and consolidation regimens, the outcome of adults with T-LBL/ALL (characterized by a presentation with extramedullary tumor) randomized to receive maintenance chemotherapy combined with prophylactic cranial irradiation after a re-induction course or HDT and ASCT. In addition, LBL patients with leukemic involvement and exhibiting one of the unfavorable characteristics such as age > 35 years, leukocytosis >30×10^9/L or failure to achieve complete remission (CR) in the bone marrow after one induction course received late re-induction and intensified conditioning before ASCT.

Design and Methods

Patients

Patients 15 to 59 years old were eligible for inclusion in the T-LBL/ALL GOELAL02 trial if they had untreated T-LBL, defined by extramedullary tumoral infiltration, with or without leukemic involvement (group A). However, according to ALL poor-risk prognostic criteria established at the beginning of this protocol,[9] patients with LBL, bone marrow involvement, >35 years old, white blood cell count (WBC) >30×10^9/L or not in bone marrow CR after the first induction course were designated as group B and received the same induction and consolidation but therefore intensified therapy according to the LAL-GOELAL02 trial.[10]

Diagnosis

The diagnosis was established by histology and immunohistology of lymph-node or tumor biopsy. Cytological examination and flow cytometry immunophenotyping were performed on circulating or bone marrow lymphoblasts and classified according to EGIL criteria after central review. Cytogenetic results were also centrally reviewed.

Treatment

Drugs and their doses used for induction, consolidation, intensification phases of treatment or maintenance are detailed in Table 1. At diagnosis, a first randomization was conducted to assign patients to intravenous or oral steroids (40 mg/m^2/day) for induction and served mainly to register every patient. Unpurged stem cells were collected, mainly from bone marrow, 2 weeks after the third course.

At this time, patients from group A were randomized again to receive either late re-induction followed by maintenance chemotherapy or HDT and ASCT. Only patients randomized to the maintenance arm received central nervous system prophylaxis consisting of two additional intrathecal methotrexate and methylprednisolone injections, and cranial irradiation with 18 Gy. The HDT conditioning regimen included cyclophosphamide (120 mg/kg) and total body irradiation (TBI) of 12 Gy in six fractions.

All patients in group B received the same late re-induction regimen followed by an intensified conditioning regimen with etoposide (40 mg/kg) in addition to cyclophosphamide and TBI with subsequent ASCT or allogeneic bone marrow transplantation (BMT) for patients under 50 years old with an HLA-matched sibling donor. None of the patients received mediastinal irradiation.

Response criteria

Response to treatment was evaluated on day 35 and at the end of the first course of consolidation. CR was defined as complete disappearance of all tumor masses assessed by computed tomography scans. When the mediastinal response was incomplete but at least 70% tumor regression was observed on day 35, a second chemotherapy regimen was initiated according to the protocol. To remain enrolled in the study, all patients had to achieve CR by the end of the second chemotherapy course.

Statistical methods

Sample size

The T-LBL/ALL GOELAL02 trial was part of a larger multicenter GOELAMS study designed to evaluate the impact of early allogeneic BMT or delayed unpurged ASCT for adult ALL[10] and the sample size was calculated on this population. Given the rarity of adult T-LBL, we report here the results of our prospective study on LBL patients treated uniformly in the T-LBL/ALL GOELAL02 trial.

Analysis

All primary analyses were conducted using the intention-to-treat rule. We compared the frequencies of risk factors between groups using a χ^2 or Fisher's exact test when necessary. Overall survival (OS) was defined as the time from first randomization to death or date of last

Table 1. Chemotherapy schedule according to the T-LBL/ALL GOELAL02 trial.

	Route	Dose	Days
Pretreatment prednisolone	IV	40 mg/m^2	-3 to -1
Course I: Induction			
Prednisone/prednisolone	PO/IV	40 mg/m^2	1-21
Vincristine	IV	1.5 mg/m^2	1, 8, 15, 22
Idarubicin	IV	5 mg/m^2	1, 8, 15, 22
L-Asparaginase	IV	7500 IU/m^2	10, 13, 16, 19, 22, 25
Methotrexate	IT	10 mg/m^2	3
Methylprednisolone	IT	40 mg	3
Course II: Consolidation (day 35 after induction)			
Cyclophosphamide	IV	650 mg/m^2	1, 15, 29
Cytarabine	IV	75 mg/m^2	3-6, 10-13, 17-20, 24-27
6-Mercaptopurine	PO	60 mg/m^2	1-28
Methotrexate	IT	10 mg/m^2	3, 10, 17, 24, 31
Methylprednisolone	IT	40 mg	3, 10, 17, 24, 31
Course III (day 70 after induction)			
Methotrexate	IV 4 hrs	3000 mg/m^2	1, 10
Folinic acid	IV	25 mg/m^2/6h	2-4, 11-13
Randomization day 90: ASCT *vs* re-induction + maintenance therapy (group A)			
Course IV: Re-induction (day 90) (group A randomized for maintenance therapy, group B)			
Dexamethasone	PO	10 mg/m^2	1-28
Vincristine	IV	1.5 mg/m^2	1, 8, 15, 22
Idarubicin	IV	5 mg/m^2	1, 8, 15, 22
Cyclophosphamide	IV	650 mg/m^2	29
Cytarabine	IV	75 mg/m^2	31-34, 38-41
6-Thioguanine	PO	60 mg/m^2	29-42
Day 90 HDT before ASCT (randomized group A patients)			
Cyclophosphamide	IV	120 mg/kg	
Total body irradiation	Fract.	12 Gy	
Day 150 intensified HDT before ASCT (group B)			
Etoposide	IV 8 h	40 mg/kg	
Cyclophosphamide	IV	120 mg/kg	
Total body irradiation	Fractionated		12 Gy
Maintenance therapy for 2 years (randomized patients from group A)			
Purinethol	PO	60 mg/m^2/day	
Methotrexate	PO	20 mg/m^2/week	

IV: intravenous injection; PO: per os; IT: intrathecal; Fract.: fractionated.

Table 2. Characteristics of patients according to their group.

Parameters	*Total*	*Group A*	*Group B*	*Maintenance*	*ASCT*
Patients, n.	45	30	15	17	10
Median age (y)	27	25	28	2	21
35 y or older, n. (%)	13 (29)	8 (27)	5 (33)	4 (24)	2 (20)
Sex ratio M/F	1.8	1.7	2	1.4	2.3
Median WBC (x 10^9/L)	14	11	66	11	9
≥30×10^9/L	13 (29)	0	13 (87)	0	0
≥100×10^9/L	3 (7)	0	3 (20)	0	0
Median platelets (×10^9/L)	229	288	59	274	273
Platelets <50×10^9/L	6 (13)	1 (3)	5 (33)	1 (6)	0
LDH over 1N, n (%)	33 (73)	20 (67)	13 (87)	14 (82)	5 (50)
Performance status					
0-1	36 (80)	26 (87)	10 (67)	15 (88)	7 (70)
2-3	9 (20)	4 (13)	5 (33)	2 (12)	3 (30)
IPI > 2	12 (27)	4 (13)	8 (53)	2 (12)	2 (20)
BM involvement	29 (64)	14 (47)	15 (100)	9 (53)	4 (40)
Mediastinal tumor	41 (91)	26 (87)	15 (100)	15 (88)	9 (90)
Bulk > 7 cm	25 (56)	17 (57)	8 (53)	9 (53)	6 (60)
Splenomegaly	12 (27)	5 (17)	7 (47)	2 (12)	2 (20)
Hepatomegaly	7 (16)	2 (7)	5 (33)	0	2 (20)
CNS involvement	3 (7)	2 (7)	1 (7)	2 (12)	0
B symptoms	6 (13)	4 (13)	2 (13)	2 (12)	2 (20)
Reviewed immunophenotype	28 (62)	13 (43)	15 (100)	8 (47)	5 (50)
EGIL not classified T	10 (36)	5 (38)	5 (33)	3 (38)	2 (40)
TII	8 (29)	3 (23)	5 (33)	1 (13)	2 (40)
TIII	8 (29)	5 (38)	3 (20)	4 (50)	1 (20)
T IV	2 (7)	0	2 (13)	0	0
CR at day 35	32 (71)	20 (67)	12 (80)	13 (76)	7 (70)
CR at day 70	40 (89)	28 (93)	12 (80)	17 (100)	10 (100)
7-year OS, % (SE)	64 (7)	65 (9)	60 (13)	65 (12)	70 (14)
7-year RFS, % (SE)	65 (8)	64 (9)	67 (14)	65 (12)	60 (15)

SE indicates standard error.

follow-up. Relapse-free survival (RFS) was defined as the time from the date of documented CR to the date of events, such as relapse or death from any cause, loss from follow-up or to the date of the last visit.

Survival curves were estimated using the Kaplan-Meier method and differences were analyzed with the log-rank test. All tests were two-sided, with p values <0.05 considered to be statistically significant. The median follow-up time was estimated by reversing the codes for the censoring indicator in a Kaplan-Meier analysis. The last date of follow-up was July 1, 2004.

Logistic regression analysis and Cox proportional hazards regression models were applied, respectively, to select and retain the risk factors significantly affecting the CR rate and time to events. SPSS (Chicago, IL, USA) software version 10.1.3 for Windows was used for these analyses.

Results

Pretreatment characteristics

Between September 1994 and December 1998, 45 consecutive patients with LBL with (n = 29) or without (n = 16) bone marrow involvement from 19 institutions were randomized in the T-LBL/ALL GOELAL02 trial. These patients' main initial characteristics are listed in Table 2.

According to the inclusion criteria, every patient had

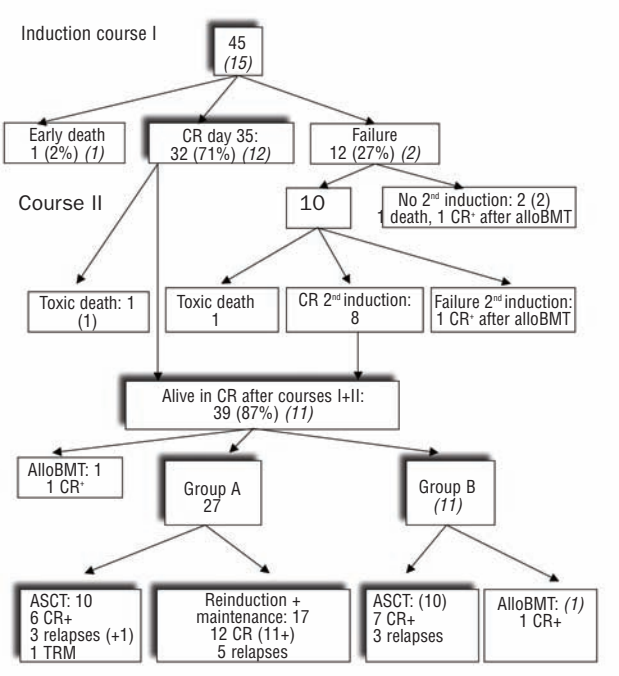

Figure 1. Flow chart of the 45 patients. +: number of patients still alive; CR: complete remission; TRM: transplant-related mortality; n: number of patients included in group B.

T-LBL defined by immunohistology or flow cytometry. Immunophenotyping was reviewed in 28 out of 29 patients (96%) with bone marrow involvement (68% of cases) (Table 2). Karyotype analysis was performed for 27 of these 29 patients (93%). Clonal cytogenetic abnormalities were observed in 59% (16/27) of them, and in all cases included structural rearrangements. Four (15%) patients exhibited low hyperdiploidy.[47-49] Five (19%) patients had complex abnormalities (≥ 3 abnormalities) and four (15%) patients had a T-cell-specific translocation involving the T-cell receptor genes including two cases of t(10;14)(q24;q11), one case of t(8;14)(q24;q11) and one case of t(11;14)(p15;q11).

Most of the structural abnormalities were unbalanced and involved chromosomes 7, 9, and/or 11, 1p and 6q. Cytogenetic analyses were performed on a lymph node biopsy for one of the 16 patients without bone marrow involvement and revealed del(6)(q?).

Treatment results

Induction and consolidation

Forty (89%) of 45 eligible patients achieved CR (Figure 1). Thirty-two (71%) patients achieved CR after the first course of induction, one patient died of infection before the day-35 bone marrow evaluation and 12 (27%) patients failed to achieve CR after the first induction course. Two of these 12 patients did not receive the second chemotherapy course: one died in progression, the other was excluded from the protocol and received allogeneic BMT after salvage chemotherapy and is still in CR. CR was obtained after the second course of chemotherapy in eight out of ten patients; treatment was interrupted because of cerebral venous thrombosis related to antithrombin III deficiency in one patient who subsequently died of progressive disease and another patient failed to achieve CR but is alive after receiving an unrelated allogeneic BMT. One patient in CR after induction died of pneumonia. After the second chemotherapy course, 39 (87%) patients were alive in CR and able to receive the planned treatment. As expected, no significant differences were observed in pretreatment characteristics, CR rate or outcome between the patients divided according to the first randomization (intravenous or oral steroids) (*data not shown*). Thirty LBL patients with or without bone marrow involvement but under 35 years old, with WBC <30×10^9/L and in bone marrow CR after the first chemotherapy course formed group A. Fifteen patients with bone marrow involvement and older than 35 years old (n=5) or with initial WBC ≥ 30×10^9/L (n=13) or not in CR after induction (n=3) were included in group B. By definition, all group B patients had BM involvement (as opposed to 47% in group A) and therefore higher WBC counts and lower platelet counts. These patients also had poorer performance status and higher lactate dehydrogenase (LDH) levels and International Prognostic Index (IPI) scores, but the differences were not statistically significant (Table 2).

Post-CR treatment

Twenty-seven LBL patients alive in CR from group A were randomized, after two courses of high dose methotrexate consolidation, to receive re-induction and maintenance therapy (n=17) or HDT and ASCT (n=10). Their step-by-step evolution is shown in Figure 1. One patient relapsed just before intensification while another relapsed before maintenance therapy. One patient died from septicemia on day 21 after ASCT. In addition, one patient was not randomized but received allogeneic BMT because of a concomitant myeloproliferative disorder and is still in CR. All were included in the analysis according to the intent-to-treat rule. According to the protocol, 11 patients from group B were not included in the second randomization but followed the ALL-GOELAL02 trial. Ten of these patients received intensified HDT and ASCT after re-induction. One patient under 50 years old with an HLA-matched sibling donor received an allogeneic BMT and is alive in CR. Most of the patients who underwent HDT received bone marrow stem cells (n=16) while four were transplanted with peripheral blood stem cells.

Remission duration and survival

At the time of analysis, the median follow-up was 7.1 years. The median OS for the entire population has not yet been reached with a 7-year OS of 64% (SE 7%) (Figure 2A) and a 7-year RFS of 65% (SE±8%) for the 40 patients in CR after the first two courses (Figure 2B).

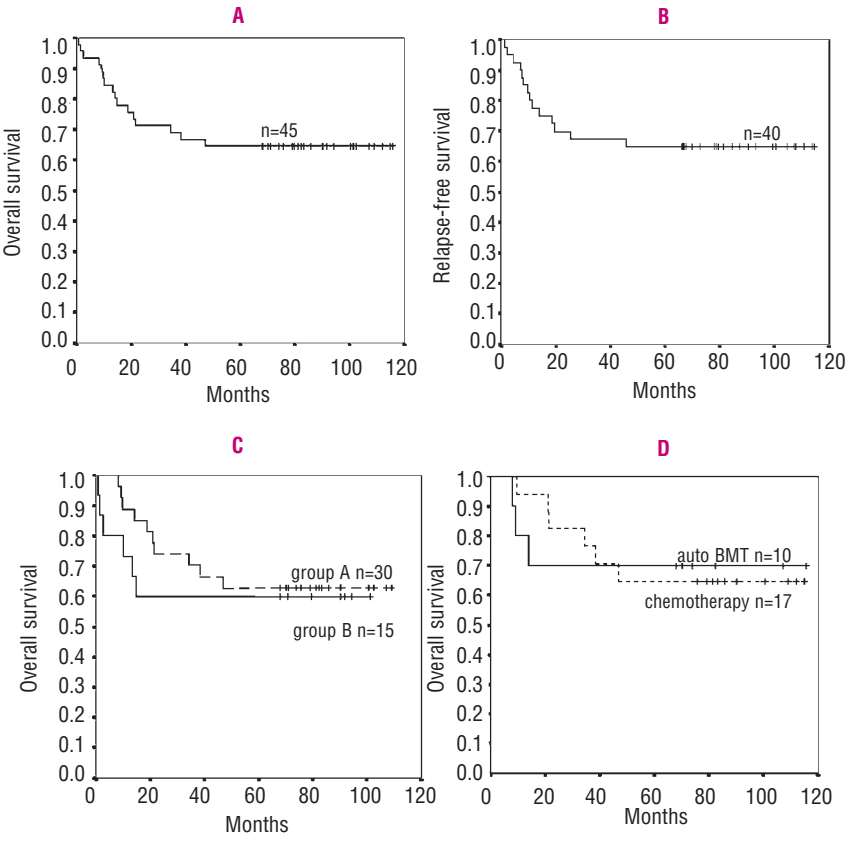

Figure 2. Survival curves. (A) OS of the entire population (n=45). (B) RFS (n=40). (C) OS according to patients' characteristics (group A and B). (D) OS according to the type of randomized consolidation and maintenance (group A, n=27).

Eleven (28%) relapsed at a median time of 10 months (range 2-24 months) after achieving CR with the median survival after relapse being 3.1 months (range 0.5-60 months). The median time to relapse was shorter after HDT and ASCT (3.8 months; range 1.9-6.2 months; n=6) than after maintenance therapy (16.4 months; range 1-22; n=5). Four patients achieved a second CR and three patients survived longer than 1 year after relapse.

Prognostic factors for remission and survival.

None of the following prognostic factors significantly influenced the remission-induction rate: age, sex, performance status (0-1 *vs* 2-4), IPI, presence or absence of fever or infection, splenomegaly, hepatomegaly, mediastinal mass, lymphadenopathy, bulky disease, initial platelet count (>100×10^9/L), WBC (>30×10^9/L), LDH level, immunophenotypic subtype, or stage (I/II *vs* III/IV).

Group A and B patients had similar response rates. However, patients without bone marrow involvement more often required two chemotherapy courses to achieve CR compared to those with bone marrow involvement with respective CR rates after induction of 56% and 79% contrasting with CR rates after the second chemotherapy course of 94% and 86%, respectively. Survival according to initial presentation and treatment received is presented in Table 3. The 7-year OS of groups A and B did not differ significantly (69% and 60%, respectively) (Figure 2C) with respective 7-year RFS rates of 64% and 67%. The OS and RFS of group A patients, evaluated according to the intent-to-treat rule, were similar after randomization to receive HDT and ASCT (n=10) or re-induction + maintenance therapy (n=17) (Figure 2D). OS and RFS did not vary significantly according to age, WBC, LDH, IPI, stage or level of bone marrow involvement. Pertinently, eight patients who achieved CR only after two induction courses had significantly better OS (p=0.04) than those entering CR after the first induction (Table 3). Among these eight patients who achieved CR after the second course, three did not have mediastinal involvement while five patients with (n=2) or without (n=3) partial bone marrow involvement (< 10%) achieved bone marrow CR after the first course but mediastinal CR only after the second course. The three patients with central nervous system but not bone marrow involvement at diagnosis achieved CR and were randomized to receive consolidation and maintenance chemotherapy; they are still alive in bone marrow CR after the first course of chemotherapy. Two other patients developed central nervous system and hematologic relapses 2 and 8 months after CR, despite our central nervous system prophylaxis regimen.

Discussion

The T-LBL/ALL GOELAL02 trial prospectively collected data on the outcome of adults with T-LBL with or without bone marrow involvement randomized to

receive maintenance chemotherapy or HDT with ASCT after an ALL-like induction regimen. In addition, according to prognostic criteria accepted at the time this ALL trial was started,[9] patients with mediastinal involvement, bone marrow involvement and age >35 years, WBC ≥30×10^9/L or not in CR at day 35 received a second chemotherapy course. For these patients, once CR was obtained, an intensified conditioning regimen followed by ASCT was given after additional re-induction.

For the 45 patients included in this trial, the 7-year OS and RFS were 64% and 65%, respectively; these results are at least as good as those obtained in the three other main prospective studies on adult LBL in which OS rates were 66%, 51% or 46% in 33, 45 and 119 patients, respectively.[7,11,12] However, our population was more homogenous in terms of characteristics and treatment received. Indeed, we included only patients with T-LBL while the European and American trials included 32% and 20%, respectively, of patients with non-T LBL, a disease which clearly evolved differently from T-LBL.[1] In addition, their treatment regimens were less homogenous. In the German study, seven patients received the 04/89 trial consolidation while 38 received that of the 05/93 trial.[7] Similarly, to increase recruitment, the European trial[11] included three groups of 83, 17 and 19 patients who received different induction chemotherapy and conditioning regimens.

The clinical and biological features of LBL in our population, such a predilection for males and a high rate of mediastinal involvement, were similar to those reported previously. However, we included more patients with bone marrow involvement (64%) than in the other main studies, in which 31, 15 and 21% of patients had bone marrow involvement.[7,11,12] Different criteria, such as the extent of nodal disease, the degree of bone marrow involvement and the presence of circulating blast cells have been used to define T-LBL and T-ALL. It is now widely accepted that LBL and ALL represent different manifestations of the same underlying disease. In agreement with this concept, we did not observe any survival differences between patients with and without bone marrow involvement.

As previously reported, between 1-2% of patients with T-LBL simultaneously have a myeloproliferative disease with hypereosinophilia.[7,12] Our patient with this condition underwent allogeneic BMT and is still in CR of both proliferations.

The GOELAL02 induction,[10] derived from the BFM,[9] induced a high CR rate (71%) similar to those previously reported[3,4,7,13-16] and increased to 89% after the second chemotherapy course. As previously reported,[12] patients without bone marrow involvement had a lower CR rate after induction (56%) but achieved similar overall response rates (94%) after the second chemotherapy course. Whether this difference in response rates reflects cell-cycle kinetics should be evaluated in future studies.

Although it has been clearly demonstrated that an ALL-like induction regimen[4,7,8,16,17] induces higher CR rates in T-LBL/ALL patients than do conventional or intensive NHL protocols,[2-5,11,14,18-20] the major, unresolved question in the management of T-LBL/ALL remains the consolidation regimen. Indeed, despite obtaining overall CR rates of 80% after administration of an ALL-type regimen in most studies, the less than 50% disease-free survival (DFS) remains disappointing.[2] Although allogeneic BMT has been performed in selected LBL patients in CR with DFS around 74% (59-91%),[4,11,21] larger registry studies reported 5-year OS rates of 49% and 42% because of high transplant-related mortality.[22,23] Therefore, allogeneic BMT was considered in our trial only in relapse or for young patients with refractory disease. The respective contributions of maintenance chemotherapy or HDT and ASCT in adult T-LBL/ALL

Table 3. CR, OS and RFS rates as a function of clinical and biological characteristics.

	CR1		Overall CR	7-year OS	7-year RFS
	N. (%)	N. (%)	N. (%)	% (SE) [p]	% (SE) [p]
Patients	45 (100)	32 (71)	40 (89)	64 (7)	65 (8)
Age					
<35 years	32 (71)	23 (72)	29 (91)	72 (8) [.15]	68 (9)
>35 years	13 (29)	9 (69)	11 (85)	46 (14)	54 (15)
WBC count					
<30×10^9/L	32 (71)	22 (69)	30 (94)	65 (8)	63 (9)
≥30×10^9/L	13 (29)	10 (77)	10 (77)	62 (13)	70 (14)
Platelet count					
≥100×10^9/L	32 (71)	20 (63)	28 (88)	63 (9)	63 (9)
<100×10^9/L	13 (29)	12 (92)	12 (92)	69 (13)	67 (14)
Myeloid antigen expression					
Present	7 (25)	6 (86)	6 (86)	21 (17)	25 (20)
Absent	21 (75)	18 (86)	19 (90)	71 (10)	68 (11) [.18]
LDH					
Normal	12 (27)	4 (33)	10 (83)	58 (14)	50 (16)
Increased	33 (73)	28 (85)	30 (91)	67 (8)	70 (8)
Performance status					
0-1	36 (80)	25 (69)	33 (92)	64 (8)	61 (9)
2-3	9(20)	7 (78)	7 (78)	67 (16)	86 (13)
IPI					
<2	17 (38)	6 (35)	14 (82)	65 (12)	57 (13)
≥2	28 (62)	26 (93)	26 (93)	64 (9)	69 (9)
Stage					
I/II	8 (18)	3 (38)	7 (88)	75 (15)	71 (17)
III/IV	37 (82)	29 (78)	33 (89)	62 (8)	64 (8)
BM involvement					
No	16 (36)	9 (56)	15 (94)	69 (12)	67 (12)
Yes <20%	5 (11)	2 (40)	4 (80)	80 (18)	75 (22)
Yes ≥20%	24 (53)	21 (88)	21 (88)	58 (10)	65 (11)
Number of courses to reach CR					
1	32 (71)	nr	nr	59 (9)	59 (9)
2	8 (18)	nr	nr	100 [.043]	88 (12)
Group					
A	30 (67)	20 (67)	28 (93)	69 (12)	64 (9)
B	15 (33)	12 (80)	12 (80)	60 (13)	67 (14)

CR indicates complete remission, CR1; complete remission after one induction course; RFS: relapse-free survival; nr: not relevant.

patients in first CR had to be evaluated. HDT performed after a less intensive, NHL-like regimen, including short-term weekly chemotherapy (MACOP-B, VACOP-B)[24] or high-dose NHL-anthracycline-containing regimen[5,25] has been disappointing with 3-year, 5-year and 5-year OS of 48%, 32%, and 46%, respectively, suggesting that the quality of the response had to be improved. In the T-LBL/ALL-GOELAL02 trial, improved OS and RFS were observed in patients who received HDT and ASCT after ALL-like induction and consolidation regimens or who received maintenance therapy after one course of re-induction. This is in agreement with the results of the European trial.[11]

Nevertheless, HDT could have several positive effects, as it might help avoid mediastinal irradiation and its long-term sequelae. Despite the absence of mediastinal irradiation, the rate of relapse in the mediastinum in the T-LBL/ALL-GOELAL02 trial was not higher than that in patients who received conventional ALL-like chemotherapy[9] followed by prophylactic mediastinal irradiation with 24 Gy (4/40 *vs* 7/42). These findings are in agreement with results obtained in children, in whom an intensive sequential consolidation regimen led to 7% mediastinal recurrence mostly without mediastinal irradiation[6] but contrast with those of the MD Anderson experience of significantly improved freedom from progression after mediastinal radiotherapy in a retrospective non-randomized study.[8] HDT also contributes to shortening the duration of chemotherapy for LBL, which can improve the quality of life of these typically young patients, except for young females in whom fertility may be a major issue. Finally, during the 7 years of follow-up of our study, no relapse occurred beyond 1 year post-HDT while some patients given maintenance therapy suffered relapses after 2 years of CR.

As in most of others reports on LBL, classical prognostic factors of ALL or NHL failed to show any prognostic significance in this trial. We did not confirm the poor outcome associated with bone marrow involvement discribed in a recent cohort of 27 patients.[26] The observation that a small subset of patients who responded slowly after induction and required a second chemotherapy course to achieve CR had better OS remains to be clarified but is in agreement with the observation by Thomas *et al*. that a slow response to induction chemotherapy did not have a poor prognistic significance.[12] It is to be hoped that the large trial conducted by the French-Swiss-Belgian Cooperative GRAALL group, currently in progress, will address these points and determine the prognostic value of karyotype, molecular analysis, and early response assessed by ^{18}F-fluorodesoxyglucose positron emission tomography.

Authors' Contributions

MH: designed the study, analyzed the data, wrote the paper, included patients in the study; MT-G: designed the sudy, analyzed the data, wrote the paper; DC, J-LH, SB, CH, DG, CB, PC, MD, J-YC, TL, J-PJ, BD, BL, FG, PS-C, BU, AT, MA-V and PB: included patients; LB: performed cytogenetic analysis; M-CB, NI: drafted the study, performed the immunophenotyping analysis, analyzed the data; EG: analyzed the data, revised the manuscript.

Conflict of Interest

The authors reported no potential conflicts of interest

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