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Pediatric-Inspired Therapy in Adults With Philadelphia Chromosome–Negative Acute Lymphoblastic Leukemia: The GRAALL-2003 Study

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The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Retrospective comparisons have suggested that adolescents or teenagers with acute lymphoblastic leukemia (ALL) benefit from pediatric rather than adult chemotherapy regimens. Thus, the aim of the present phase II study was to test a pediatric-inspired treatment, including intensified doses of nonmyelotoxic drugs, such as prednisone, vincristine, or L-asparaginase, in adult patients with ALL up to the age of 60 years.

Patients and Methods
Between 2003 and 2005, 225 adult patients (median age, 31 years; range, 15 to 60 years) with Philadelphia chromosome–negative ALL were enrolled onto the Group for Research on Adult Acute Lymphoblastic Leukemia 2003 protocol, which included several pediatric options. Some adult options, such as allogeneic stem-cell transplantation for patients with high-risk ALL, were nevertheless retained. Results were retrospectively compared with the historical France-Belgium Group for Lymphoblastic Acute Leukemia in Adults 94 (LALA-94) trial experience in 712 patients age 15 to 55 years.

Results
Complete remission rate was 93.5%. At 42 months, event-free survival (EFS) and overall survival (OS) rates were 55% (95% CI, 48% to 52%) and 60% (95% CI, 53% to 66%), respectively. Age remained an important bad prognostic factor, with 45 years of age as best cutoff. In older versus younger patients, there was a higher cumulative incidence of chemotherapy-related deaths (23% *v* 5%, respectively; $P < .001$) and deaths in first CR (22% *v* 5%, respectively; $P < .001$), whereas the incidence of relapse remained stable (30% *v* 32%, respectively). Complete remission rate ($P = .02$), EFS ($P < .001$), and OS ($P < .001$) compared favorably with the previous LALA-94 experience.

Conclusion
These results suggest that pediatric-inspired therapy markedly improves the outcome of adult patients with ALL, at least until the age of 45 years.

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INTRODUCTION

In children with acute lymphoblastic leukemia (ALL), current therapies yield complete remission (CR) rates of 98% and event-free survival (EFS) rates of 70% to 80% at 5 years.[1] In adults, even if the CR rate reaches 85% to 90%, therapeutic results remain less satisfactory, with a disease-free survival (DFS) rates of only 30% to 40% at 5 years.[1] The largest adult trial conducted by the British Medical Research Council (MRC) and Eastern Cooperative Oncology Group (ECOG) has recently reported a 90% CR rate with a 5-year overall survival (OS) rate of 43% in patients with Philadelphia chromosome (Ph)–negative ALL.[2] In a study that retrospectively compared two trials, one designed for children and the other for adults, we have reported that adolescents and young adults age 15 to 20 years old markedly benefited from a pediatric approach.[3] Comparable results have been reported in four similar studies.[4-7] However, whether pediatric or pediatric-inspired treatments might also improve the outcome of adults older than age 20 years remained unresolved. The main concern was the perceived worse tolerance of higher cumulative doses of chemotherapy.

Table 1. GRAALL-2003 Chemotherapy

Agent	Dose
Remission induction	
Corticosteroid prephase	
PDN	60 mg/m^2/d on days –7 to –1
IT MTX	15 mg between days –7 and –4
Induction course	
PDN	60 mg/m^2/d on days 1-14
DNR	50 mg/m^2/d on days 1, 2, and 3; 30 mg/m^2/d on days 15 and 16
VCR	2 mg on days 1, 8, 15, and 22
L-asparaginase*	6,000 U/m^2/d on days 8, 10, 12, 20, 22, 24, 26, and 28
CPM	750 mg/m^2/d on day 1; 750 mg/m^2/d on day 15 in good early responders; 500 mg/m^2/12 h on days 15 and 16 in poor early responders
Lenograstim	150 μg/m^2/d from day 17 to myeloid recovery
Salvage course	
IDA	12 mg/m^2/d on days 1-3
Ara-C	2 g/m^2/12 h on days 1-4
Lenograstim	150 μg/m^2/d from day 9 to myeloid recovery
Consolidation blocks	
Blocks 1, 4, and 7	
Ara-C	2 g/m^2/12 h on days 1 and 2
DXM	10 mg/12 h on days 1 and 2
L-asparaginase*	10,000 U/m^2 on day 3
Lenograstim	150 μg/m^2/d on days 7-13
Blocks 2, 5, and 8	
MTX	3 g/m^2 continuous infusion on day 15
VCR	2 mg on day 15
L-asparaginase*	10,000 U/m^2 on day 16
6-MP	60 mg/m^2/d on days 15-21
Lenograstim	150 μg/m^2/d on days 22-27
Blocks 3, 6, and 9	
CPM	500 mg/m^2/d on days 29 and 30
VP-16	75 mg/m^2/d on days 29 and 30
MTX	25 mg/m^2 on day 29
Lenograstim	150 μg/m^2/d from day 31 to myeloid recovery
Late intensification (between consolidation blocks 6 and 7)	
For patients in CR after the first induction course	
PDN	60 mg/m^2/d on days 1-14
VCR	2 mg on days 1, 8, and 15
DNR	30 mg/m^2/d on days 1-3
L-asparaginase*	6,000 U/m^2/d on days 8, 10, 12, 18, 20, and 22
CPM	500 mg/m^2/12 h on day 15
Lenograstim	150 μg/m^2/d if neutrophils $<$ 0.5 G/L to myeloid recovery
For patients in CR after the salvage course	
IDA	9 mg/m^2/d on days 1-3
Ara-C	2 g/m^2/12 h on days 1-4
Lenograstim	150 μg/m^2/d from day 9 to myeloid recovery
Maintenance therapy	
PDN	40 mg/m^2/d on days 1-7 monthly for 12 months
VCR	2 mg on day 1 monthly for 12 months
MTX	25 mg/m^2/wk orally for 24 months
6-MP	60 mg/m^2/d for 24 months
CNS therapy	
Prophylaxis	
Triple IT injections†	One at days 1 and 8 of induction; one at day 29 of each series of consolidation blocks; one at day 1 of late intensification
Cranial irradiation	18 Gy before maintenance therapy initiation; 6-MP 60 mg/m^2/d during irradiation
Treatment of patients with initial CNS involvement	
Triple IT injections†	Eight between days −7 and 21 of induction; four during the first two consolidation blocks; one at day 29 of consolidation blocks 3 and 6
Cranial irradiation	15 Gy before SCT or 24 Gy before maintenance therapy initiation; 6-MP 60 mg/m^2/d during irradiation

Abbreviations: GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; PDN, prednisone; IT, intrathecal; MTX, methotrexate; DNR, daunorubicin; VCR, vincristine; CPM, cyclophosphamide; IDA, idarubicin; Ara-C, cytarabine; DXM, dexamethasone; 6-MP, 6-mercaptopurine; VP-16, etoposide; CR, complete remission; SCT, stem-cell transplantation.

**Escherichia coli* L-asparaginase.

†Triple IT injections consisted of MTX 15 mg, Ara-C 40 mg, and methylprednisolone 40 mg.

Thus, the aim of the present phase II study conducted by the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) was to test the efficacy and tolerability of a pediatric-inspired therapy in adults with Ph-negative ALL up to the age of 60 years. When retrospectively compared with the historical France-Belgium Group for Lymphoblastic Acute Leukemia in Adults 94 (LALA-94) trial experience,[8] results suggest that this strategy might be associated with a highly significant improvement in patient outcome, even if a worse treatment tolerance is observed in patients older than 45 years.

PATIENTS AND METHODS

Study Design and Population

The GRAALL-2003 study was conducted in 70 centers in France, Belgium, and Switzerland. Patients age 15 to 60 years old were eligible if they had newly diagnosed Ph-negative ALL with L1 or L2 morphology according to the French-American-British classification. Ineligibility criteria were severe cardiac disease; renal or hepatic dysfunction; HIV, human T-lymphotropic virus, hepatitis B virus, or hepatitis C virus infection; and pregnancy. A total of 225 consecutive patients were entered onto the study between November 2003 and November 2005. Written informed consent was obtained from all patients or from the parents of those younger than 18 years old before enrollment. The study was approved in March 2003 by the Institutional Review Board of Hôpital Purpan, Toulouse II, France, and conducted in accordance with the Declaration of Helsinki.

Diagnosis of ALL

Baseline evaluation included ALL morphology, immunophenotyping, DNA index measurement, cytogenetics, molecular analysis, and HLA typing. Molecular analysis with real-time quantitative polymerase chain reaction or competitive polymerase chain reaction–based Genescan (Applied Biosystems, Foster City, CA)[9,10] allowed for the detection of *BCR-ABL*, *MLL-AF4*, or *E2A-PBX1* fusion transcripts and for immunoglobulin heavy-chain and T-cell receptor gene rearrangements used to monitor minimal residual disease (MRD). The threshold of 10^{-2} (2-log reduction from diagnosis sample) was used to define high-level MRD after CR induction. Patients diagnosed with Ph- and/or *BCR-ABL*–positive leukemia were entered onto another specific study.[11]

Response Criteria

Corticosteroid sensitivity was defined as a peripheral-blood blast cell count lower than 1.0×10^9/L after the 7-day corticosteroid prephase. Chemotherapy sensitivity was defined as a bone marrow blast cell percentage less than 5% after the first week of chemotherapy.[8] Poor early responders were defined as patients with corticosteroid-resistant (CsR) and/or chemotherapy-resistant (ChR) ALL. Hematologic CR was defined according to standard criteria.

Risk Classification and Stratification

Baseline high-risk factors were a WBC count of $\geq 30 \times 10^9$/L for B-lineage ALL, clinical and/or morphologic CNS involvement, t(4;11) and/or *MLL-AF4* fusion transcript, t(1;19) and/or *E2A-PBX1* fusion transcript, and low hypodiploidy (30 to 39 chromosomes or DNA index < 0.85) and/or near-triploidy (60 to 78 chromosomes or DNA index of 1.30 to 1.69).[12] Response-based high-risk factors were CsR and/or ChR, absence of CR after the first induction course, and high MRD level at CR. All patients with at least one baseline or response-based high-risk factor were classified in the high-risk ALL subgroup. All other patients were in the standard-risk ALL subgroup. The treatment was influenced by these risk factors at two different stages, as follows: poor early responders were offered early induction reinforcement; and patients $\leq$ age 55 years with high-risk ALL were eligible for allogeneic stem-cell transplantation (SCT) if they had an identified matched related or 10/10 allelic-matched unrelated donor.

Treatments

Poor early responders received an induction reinforcement based on a sequential bolus administration of cyclophosphamide (HyperC; Table 1). A salvage course was offered to patients with resistant ALL. Consolidation started when polymorphonuclear cell and platelet counts reached 1.0×10^9/L and 100×10^9/L, respectively, as long as liver ALT and AST were less than 2.5× the upper normal limit, serum creatinine clearance was greater than 60 mL/min, and serum albumin was greater than 25 g/L. Consolidation blocks 1 to 3 and then 4 to 6 had to be administered every 2 weeks whatever the blood cell counts. The interval between blocks 3 and 4 was nevertheless adapted to hematologic recovery. Late intensification was administered between consolidation blocks 6 and 7. CNS prophylaxis included intrathecal injections and cranial irradiation. Overall, the trial comprised 16-fold more L-asparaginase, 3.7-fold more vincristine, and 8.6-fold more prednisone than the former adult LALA-94 protocol.[8] On the basis of previous adult results,[8] allogeneic SCT was proposed in first CR to high-risk patients only. Allogeneic SCT was scheduled after either the third or sixth consolidation block according to donor availability and eventually preceded by one or two interphase cycles based on methotrexate 1,500 mg/m^2 on day 1 and L-asparaginase 10,000 U/m^2 on day 2 at a 2-week interval. Conditioning regimen included total-body irradiation (12-Gy fractionated dose) and high-dose cyclophosphamide (60 mg/kg/d for 2 days). Prophylaxis of graft-versus-host disease relied on cyclosporine and methotrexate.

Statistical Considerations

Binary variables were compared with the Fisher's exact test. The Mann-Whitney *U* test was used for median comparisons. OS and EFS were calculated from the date of prephase initiation. Events accounting for EFS were failure of

Table 2. Patients Characteristics

Characteristic	No. of Patients (N = 225)
Sex	
Male	150
Female	75
Age, years	
Median	31
Range	15-60
> 35	97
15-40	147
41-60	78
ALL lineage	
B	149
T	76
CNS disease	
All patients	9
B-lineage ALL	2
T-lineage ALL	7
WBC, $\times 10^9$/L	
All patients	
Median	11.8
Range	0.7-399
B-lineage ALL	
Median	7.7
Range	0.7-348
T-lineage ALL	
Median	27.0
Range	0.9-399
Cytogenetics*	
t(4;11) and/or *MLL-AF4*	21/221
t(1;19) and/or *E2A-PBX1*	7/218
Low hypodiploidy and/or near triploidy	6/225

Abbreviation: ALL, acute lymphoblastic leukemia.
No. of patients/No. of patients tested.

CR induction, relapse, and death in first CR. DFS was calculated from the CR date. Events accounting for DFS were relapse and death in CR. Failure time data were estimated using the Kaplan-Meier method[13] and then compared using the log-rank test.[14] Cumulative incidence estimations took into account competing risks and were compared by the Gray test.[15] All deaths related to treatment toxicity during induction or later but not after SCT were collectively defined as chemotherapy-related deaths. In multivariate analyses, outcome comparisons were adjusted with the Cox model[16] and tested using the likelihood-ratio test. All calculations were performed using the STATA/SE software, version 9.0 (STATA Corp, College Station, TX) and the R software, version 1.5.1 (The R Development Core Team, A Language and Environment Copyright, 2002; University of Auckland, Auckland, New Zealand). Outcome was updated as of December 15, 2007. The median follow-up time of surviving patients was 37 months.

RESULTS

Patient Characteristics

The median age was 31 years (range, 15 to 60 years; Table 2). One hundred forty-nine patients had B-cell precursor (BCP) ALL, whereas 76 patients had T-lineage ALL. Median age was 34 years in the B-lineage subgroup and 29 years in the T-lineage subgroup ($P = .23$ by Mann-Whitney U test). Median WBC was significantly higher in the T-lineage subgroup compared with the B-lineage subgroup ($P < .001$ by Mann-Whitney U test).

Response to Initial Therapy

Overall, 57 patients (25%) had CsR-ALL, and 90 patients (40%) had ChR-ALL (Appendix Table A1, online only). Ninety-nine (89%) of the 111 poor early responders received the planned HyperC induction reinforcement. The reason for not administering this sequence was early death in one patient and toxic adverse event in the remaining 11 patients. None of the patients with corticosteroid-sensitive or chemotherapy-sensitive ALL received HyperC reinforcement. The overall CR rate was 93.5% (210 patients). The rate of CR patients who did not require the salvage course was not lower in poor early responders compared with good early responders (89% *v* 93%, respectively; $P = .48$ by Fisher's exact test). Fourteen patients (6%) died during induction, four of them after the HyperC sequence. No patient died during salvage therapy. The causes of induction death were sepsis (nine patients), CNS thrombosis and/or hemorrhage (four patients), and liver failure (one patient). The incidence of induction death was significantly higher in the B-lineage subgroup ($P = .038$ by Fisher's exact test).

Risk Groups

Among the 210 CR patients, 139 patients (66%) were classified in the high-risk subgroup (95 BCP-ALL patients and 44 T-ALL patients). Risk factors are listed in Appendix Table A2 (online only). Of note, the risk classification used in the present study differed markedly from the MRC-ECOG classification, which only took into account age (> 35 years) and WBC ($> 30 \times 10^9$/L for B lineage or 100×10^9/L for T lineage).[2] When using MRC-ECOG criteria, a total of 92 patients were in the standard-risk subset, 88 of whom reached CR. Among these 88 patients, 53 were in the high-risk subset according to GRAALL criteria. Conversely, 133 patients would have been in the high-risk subset if using the MRC-ECOG criteria, with 122 of them reaching CR. Among these 122 patients, 36 were classified as being in the standard-risk subset according to GRAALL criteria.

General Outcome

A patient flow chart is shown in Figure 1. At 42 months, EFS and OS were estimated to be 55% (95% CI, 48% to 62%) and 60% (95% CI, 53% to 66%), respectively (Fig 2). DFS was estimated to be 59%

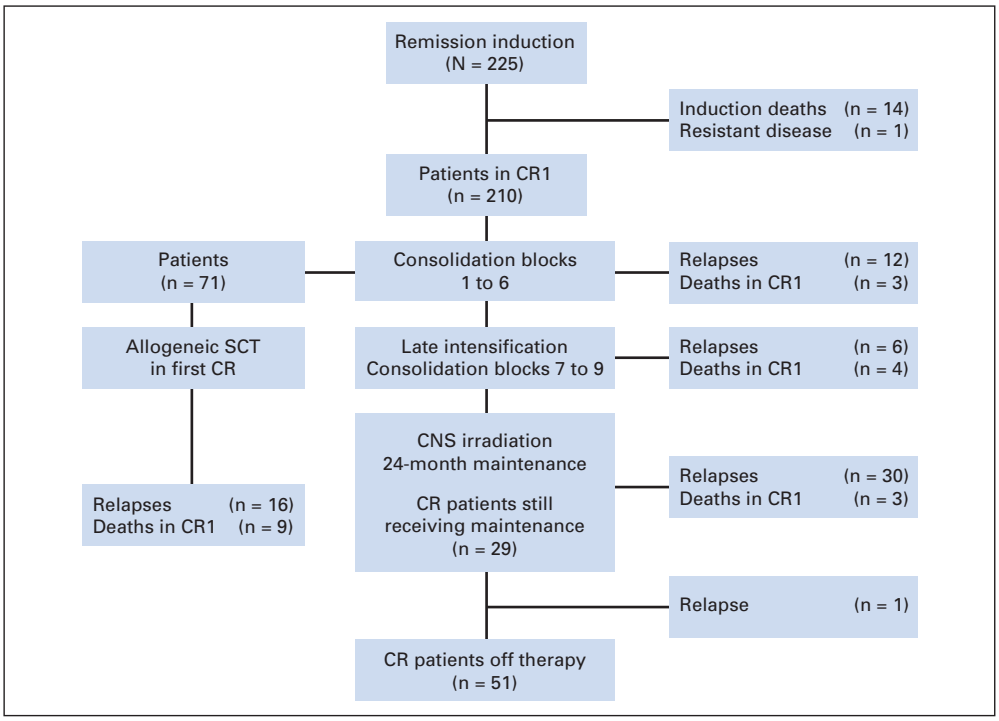

Fig 1. Patient flow chart. Among the 210 patients who reached complete remission (CR), 65 patients experienced relapse (including nine isolated CNS relapses and one combined CNS/marrow relapse), and 73 patients died, including 19 deaths in first CR (CR1). Relapses occurred during the first six-block consolidation period in 12 patients, after stem-cell transplantation (SCT) in 16 patients, or later during therapy in 37 patients. Deaths in CR1 occurred during the first six-block consolidation period in three patients, after SCT in nine patients, or later during therapy in seven patients.

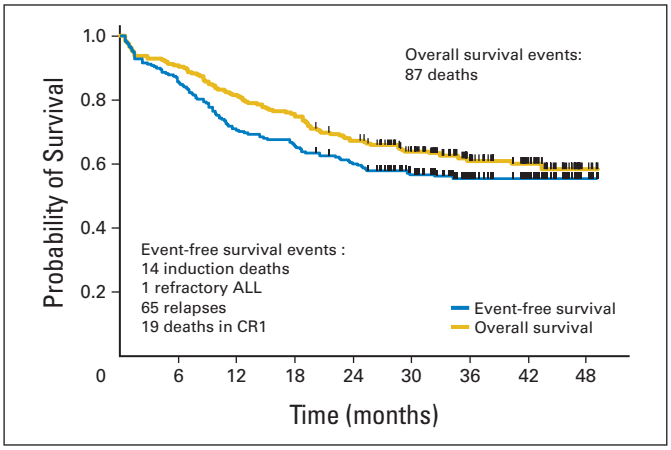

Fig 2. Event-free survival (EFS) and overall survival (OS). At 42 months, EFS was estimated to be 55% (95% CI, 48% to 62%), and OS was estimated to be 60% (95% CI, 53% to 66%). ALL, acute lymphoblastic leukemia; CR1, first complete remission.

(95% CI, 52% to 66%) at 42 months. At that time, cumulative incidence of relapse and death in first CR were estimated to be 32% (95% CI, 26% to 38%) and 9% (95% CI, 6% to 14%), respectively. All deaths in first CR were related to chemotherapy or transplantation toxicity, except for two patients who developed secondary acute myeloid leukemia and one patient who died from a non–ALL- or treatment-related event.

There was a trend toward a better outcome in patients with T-ALL. At 42 months, EFS was estimated to be 62% (95% CI, 50% to 72%) in T-ALL patients and 52% (95% CI, 42% to 59%) in BCP-ALL patients ($P = .09$ by log-rank test). This was mainly related to a higher CR rate in the T-ALL subset versus BCP-ALL patients (99% *v* 91%, respectively; $P = .02$). Once CR was achieved, 42-month DFS was estimated to be 57% (95% CI, 48% to 65%) in BCP-ALL patients and 63% (95% CI, 51% to 73%) in T-ALL patients ($P = .37$ by log-rank test). Of note, using this response-adapted induction, a poor early response still had a negative impact on DFS in patients with BCP-ALL ($P = .004$ by log-rank test) but not in those with T-ALL ($P = .23$ by log-rank test).

Impact of Risk Classification

Among the 139 CR patients with high-risk ALL, 132 were ≤ 55 years old. Of these patients, 74 had a donor, and 65 actually underwent transplantation in first CR (38 with a matched familial donor and 27 with a matched unrelated donor). Nine patients with a donor did not receive SCT in first CR because of early relapse (six patients), acquired comorbidity (two patients), or refusal (one patient). Six additional patients with a matched familial donor underwent transplantation in first CR despite the absence of any high-risk factor in five patients or an age higher than 55 years in one patient.

When censoring the 71 patients who received transplantation in first CR at transplant time, 42-month EFS, overall survival, and DFS were 55% (95% CI, 47% to 63%), 60% (95% CI, 51% to 68%), and 59.5% (95% CI, 51% to 67%), respectively. Using the GRAALL classification, DFS was 52% (95% CI, 40% to 63%) in high-risk patients *v* 68% (95% CI, 55% to 78%) in standard-risk patients ($P = .05$ by log-rank test). However, the difference in OS rate from CR among the standard- and high-risk GRAALL subgroups did not reach the significance level (60% *v* 72% at 42 months, respectively; $P = .08$). Using the MRC-ECOG classification, DFS was 54% (95% CI, 42% to 64%) in high-risk patients *v* 67% (95% CI, 53% to 77%) in standard-risk patients ($P = .06$ by log-rank test). In the MRC-ECOG standard-risk subgroup, EFS and OS were 64% (95% CI, 51% to 74%) and 76% (95% CI, 63% to 85%), respectively, after censoring at transplantation time those patients who received transplantation.

Impact of Age

Advanced age significantly influenced OS ($P = .001$ by univariate Cox analysis). The best identified age cutoff was 45 years (42-month OS, 66% *v* 41% in patients ≤ *v* > 45 years, respectively; hazard ratio = 2.2; 95% CI, 1.4 to 3.4 in the older subgroup; $P < .001$ by log-rank test). As a result of a higher induction death rate, the CR rate was lower in the older subgroup (Table 3). When taking into account SCT in first CR as a competing event, cumulative incidence of death in first CR was significantly higher in the older subgroup, whereas cumulative incidence of relapse was similar (Table 3). Causes of death in first CR were transplantation-related mortality (nine patients), sepsis (five patients), secondary acute myeloid leukemia (two patients), CNS hemorrhage (one patient), thromboembolic event (one patient), and sudden death not related to ALL therapy (one patient). The worse tolerance of induction and postremission therapy in the older subgroup led to lower EFS and OS (Table 3). This is illustrated in Appendix Figure A1 (online only), which also shows the cumulative

Table 3. Results of GRAALL-2003 Chemotherapy According to Age Subgroups

Outcome	15-45 Years (n = 172)	46-60 Years (n = 53)	*P*
Induction death			.02
No. of patients	7	7	
%	4	13	
Complete remission			.05
No. of patients	164	46	
%	95	87	
Outcome at 42 months*			
Cumulative incidence of death in first CR			.0001
%	2	15	
95% CI	1 to 6	8 to 29	
Cumulative incidence of relapse			.51
%	25	20	
95% CI	19 to 32	11 to 34	
DFS			.21
%	61	53	
95% CI	51 to 70	34 to 68	
EFS			.03
%	58	46	
95% CI	49 to 67	30 to 60	
OS			.004
%	64	47	
95% CI	54 to 72	31 to 62	

Abbreviations: GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; CR, complete remission; DFS, disease-free survival; EFS, event-free survival; OS, overall survival.

*To focus on the effects of chemotherapy, stem-cell transplantation was taken into account as a competing risk in estimating cumulative incidences, and patients who received a transplantation in first CR were censored at transplantation time in estimating DFS, EFS, and OS.

incidence of chemotherapy-related deaths over the treatment period. To focus on patients treated with chemotherapy, allogeneic SCT was considered as a competing event when estimating this cumulative incidence, and transplantation patients were censored at SCT time in the EFS curves. The difference in EFS was similar when excluding rather than censoring SCT patients (data not shown).

Older patients did not tolerate the planned treatment as well as younger patients, especially L-asparaginase, leading to a lower cumulative dose and delay in consolidation initiation in CR patients (Table 4). However, the incidence of severe drug-related adverse events was not significantly higher in the older subgroup.

Historical Comparison With the LALA-94 Trial

We then retrospectively compared the GRAALL-2003 results with those observed in patients with Ph-negative ALL treated in the former French LALA-94 adult trial (Table 5).[8] Because older patients were not included in the LALA-94 trial, the 214 GRAALL-2003 patients ≤ age 55 years old were compared with the 712 LALA-94 patients with Ph-negative ALL. Main baseline characteristics were well balanced between both trial cohorts, except for more patients with CNS disease in the LALA-94 cohort and more patients with t(4;11) and/or *MLL-AF4* rearrangements in the GRAALL-2003 cohort. Significant increases in CR, EFS, and OS rates and a significant decrease in cumulative incidence of relapse were observed in the GRAALL-2003 trial (Table 5, Fig A2A, online only). The gain in EFS was observed in patients older than 45 years as well as in younger patients (Appendix Fig A2B). However, this translated significantly into a longer OS in the younger age subgroup (66% *v* 44% at 42 months in GRAALL-2003 *v* LALA-4, respectively; $P < .001$ by log-rank test) but not in the subgroup of patients older than 45 years (42% *v* 30% at 42 months in GRAALL-2003 *v* LALA-4, respectively; $P = .13$ by log-rank test). Of importance, because indications of SCT in first CR differed among both trials, the historical inferiority of the LALA-94 protocol was still observed and even more marked when censoring all SCT patients at transplantation time in both trials (data not shown).

Table 4. Tolerance of GRAALL-2003 Chemotherapy According to Age Subgroups

Parameter	15-45 Years (n = 172)	46-60 Years (n = 53)	*P*
Remission induction chemotherapy			
Median doses actually received*			
Vincristine, mg	8	8	.80
L-asparaginase, U/m^2	48,000	36,000	.006
Prednisone, mg/m^2	824	812	.22
Adverse events, No. of patients			
All grade 1-2	148	47	.90
Grade 3-4			
Peripheral neuropathy	2	1	.56
Intolerance to L-asparaginase†	2	2	.24
Thromboembolic	5	5	.06
Liver toxicity	31	15	.12
Time to consolidation, days*			
Time to block 1			.03
Median	39	44	
Range	28-102	30-98	
Time to block 4			.03
Median	89	95	
Range	62-160	75-148	
Induction death	7	7	.02
Postremission chemotherapy‡			
Median doses actually received before maintenance§			
Vincristine, mg	12	10	.08
L-asparaginase, U/m^2	81,000	29,000	.003
Dexamethasone, mg	120	120	.47
Grade 3-4 events before maintenance therapy, No. of patients			
Peripheral neuropathy	2	1	.55
Intolerance to L-asparaginase†	5	4	.21
Thromboembolic	4	1	.99
Liver toxicity	27	9	.64
Median doses per month actually received during maintenance‖			
Vincristine, mg	1.7	1.3	.43
Prednisone, mg	387	300	.26
Mercaptopurine, mg	50	0	.47
Methotrexate, mg	126	84	.21
Death in first CR	3	7	.001

Abbreviations: GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; CR, complete remission; NA, not applicable.
*Results are shown for the 204 patients in CR after the first induction course.
†Intolerance to L-asparaginase comprised allergy and pancreatitis.
‡Results are shown for the 139 patients who did not undergo transplantation in first CR (107 patients who were 15 to 45 years old and 32 patients who were 46 to 60 years old).
§Cumulative doses are given from CR achievement until the onset of maintenance therapy.
‖Doses are given per month of maintenance therapy actually delivered.

DISCUSSION

Results presented here strongly suggest that an intensified protocol might yield significantly better results than former protocols in adults with Ph-negative ALL. This intensified approach incorporated several pediatric options including increased cumulative dosages and cautious observance of dose-intensity. The doses of nonmyelotoxic drugs (prednisone, vincristine, and L-asparaginase) were in the range of most pediatric regimens. The HyperC induction sequence might also have played a role, particularly in adults with T-ALL in whom the HyperC, vincristine, doxorubicin, and dexamethasone regimen previously yielded an excellent CR rate.[17] Late intensification, which has rarely been tested in adults,[18,19] was relatively well tolerated and might also have contributed. Not only the doses, but also the schedules and modalities of administration of the different drugs may have impacted therapeutic results. In this regard, a short delay between remission induction and consolidation has been evidenced as a prominent favorable prognostic factor in both childhood and adult ALL.[20,21] In addition to this pediatric-like chemotherapy backbone, the GRAALL-2003 protocol retained treatment options currently used in adults, including cranial irradiation, early intensive administration of growth factors, and larger indication of allogeneic SCT in first CR. Actually, given the poor outcome observed so far in adults with the disease, the issue of long-term effects was less of a concern than in children.

If these promising results could be confirmed in larger studies and/or with a longer follow-up, they will probably impact on the clinical management of these patients in the future. In younger patients with low peripheral-blood count ALL corresponding to the standard-risk MRC-ECOG group,[2] such new intensified approaches might be associated with long-term DFS rates of 65% to 70% in

Table 5. Historical Comparison Between the GRAALL-2003 and LALA-94 Trials

Characteristic or Outcome Measure	GRAALL-2003 (N = 214)	LALA-94 (N = 712)	*P*
Patient characteristics			
Age, years			.15
Median	31	29	
Range	15-55	15-55	
T-lineage ALL, %	35	35	.99
WBC $\geq 30 \times 10^9$/L in B-lineage ALL, %	29	36	.13
CNS disease, %	4	8	.03
t(4;11) and/or *MLL-AF4*, %	10	5	.02
t(1;19) and/or *E2A-PBX1*, %	3	4	.83
Low hypodiploidy and/or near triploidy	2.5	2.5	.80
Patient outcome			
Induction death rate, %	6	4.5	.37
Complete remission rate, %	93.5	88	.02
42-month cumulative incidence of relapse			< .001
%	31	55	
95% CI	25 to 38	51 to 59	
42-month cumulative incidence of death in first complete remission			.89
%	8.5	8	
95% CI	5 to 13	6 to 10	
42-month EFS			< .001
%	57	33	
95% CI	50 to 63	29 to 36	
42-month OS			< .001
%	61	41	
95% CI	54 to 68	37 to 45	

Abbreviations: GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; LALA, France-Belgium Group for Lymphoblastic Acute Leukemia in Adults; ALL, acute lymphoblastic leukemia; EFS, event-free survival; OS, overall survival.

patients who have not received transplantation, raising again the issue of the place of allogeneic SCT in first CR in these relatively good-risk patients. However, the age issue will certainly remain the most important one. Although the toxicity of the GRAALL-2003 chemotherapy was acceptable in younger adults up to 45 years of age, older patients did not tolerate both induction and postremission treatments as well. Even if they still drew a benefit from this intensified approach compared with the historical experience, the cumulative incidence of chemotherapy-related deaths of 23% is clearly too high (Fig A1, online only). Dose adaptations and reduced intensity conditioning SCT might be evaluated in these older adults.

A more radical option currently being tested by several other groups would be to use unmodified pediatric protocols in adult patients Even if preliminary results look interesting,[22,23] the main issue obviously relates to the upper age limit because it remains uncertain whether adults older than 20 to 25 years of age will tolerate such unmodified pediatric approaches as well as teenagers. Thus, currently, we propose using unmodified pediatric protocols in teenagers and adapted pediatric-inspired protocols in younger adults. To reduce treatment-related toxicity in patients older than 45 years, we are currently recommending systemic anti-infectious prophylaxis during induction and delayed intensification. Testing reduced-intensity conditioning rather than standard myeloablative SCT in these patients could be another option.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ERRATUM

The February 20, 2009, article by Huguet et al, entitled, "Pediatric-Inspired Therapy in Adults With Philadelphia Chromosome–Negative Acute Lymphoblastic Leukemia: The GRAALL-2003 Study" (J Clin Oncol 27:911-918, 2009), contained errors in Table 1.

Under "Remission induction," the term "corticosteroid prophase" was given, whereas it should have been "corticosteroid prephase." The dose for L-asparaginase was given as, "6,000 U/m^2/d on days 8, 10, 12, 18, 20, 22, 24, and 26," and it should have been, "6,000 U/m^2/d on days 8, 10, 12, 20, 22, 24, 26, and 28." Also, the dose for cyclophosphamide (CPM) was given as, "750 mg/m^2/d on days 1 and 8; 750 mg/m^2 on day 15 in good early responders; 500 mg/m^2/12 h on days 15 and 16 in poor early responders," and should have been, "750 mg/m^2/d on day 1; 750 mg/m^2/d on day 15 in good early responders; 500 mg/m^2/12 h on days 15 and 16 in poor early responders."

Under "Consolidation blocks 3, 6, and 9," the dose for CPM was given as, "500 mg/m^2 on days 29 and 30," and should have been, "500 mg/m^2/d on days 29 and 30." Also, the dose for VP-16 was given as, "75 mg/m^2m/d on days 29 and 30," and should have been "75 mg/m^2/d on days 29 and 30."

Under "Late intensification (between consolidation blocks 6 and 7)," the dose for lenograstim was not indicated for patients in complete remission after the first induction course, and should have been, "150 μg/m2/d if neutrophils $<$ 0.5 G/L to myeloid recovery."

Under "Maintenance therapy," the dose for prednisone (PDN) was given as, "40 mg/m^2/d on days 1-14 monthly for 12 months," and should have been, "40 mg/m^2/d on days 1-7 monthly for 12 months."

Under "CNS therapy, Treatment of patients with initial CNS involvement," the dose for triple IT injects was given as, "Eight between days 7 and 21 of induction; four during the first two consolidation blocks; one at day 29 of consolidation blocks 3 and 6," and should have been, "Eight between days -7 and 21 of induction; four during the first two consolidation blocks; one at day 29 of consolidation blocks 3 and 6." Also, the dose for cranial irradiation was given as, "15 Gy before SCT or 18 Gy before late intensification; 6-MP 60 mg/m^2/d during irradiation," and should have been, "15 Gy before SCT or 24 Gy before maintenance therapy initiation; 6-MP 60 mg/m^2/d during irradiation."

Also under "CNS therapy," the footnote for triple IT injections was given as:

†Triple IT injections consisted of MTX 15 mg, Ara-C 40 mg, and PDN 40 mg.

While it should have been:

†Triple IT injections consisted of MTX 15 mg, Ara-C 40 mg, and methylprednisolone 40 mg.

The online version has been corrected in departure from the print.

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