A randomized study of pegylated liposomal doxorubicin *versus* continuous-infusion doxorubicin in elderly patients with acute lymphoblastic leukemia: the GRAALL-SA1 study

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The online version of this article has a Supplementary Appendix.

ABSTRACT

Background

The prognosis of acute lymphoblastic leukemia in the elderly is poor. The GRAALL-SA1 phase II, randomized trial compared the efficacy and toxicity of pegylated liposomal doxorubicin *versus* continuous-infusion doxorubicin in patients 55 years or older with Philadelphia chromosome-negative acute lymphoblastic leukemia.

Design and Methods

Sixty patients received either continuous-infusion doxorubicin (12 mg/m^2/day) and continuous-infusion vincristine (0.4 mg/day) on days 1-4 or pegylated liposomal doxorubicin (40 mg/m^2) and standard vincristine (2 mg) on day 1, accompanied by dexamethasone, followed at day 28 by a second cycle, reinforced by cyclophosphamide. End-points were safety, outcome and prognostic factors.

Results

Myelosuppression was reduced in the pegylated liposomal doxorubicin arm with shorter severe neutropenia (P=0.05), shorter severe thrombocytopenia (P=0.03), and fewer red blood cell transfusions (P=0.04). Grade 3/4 infections and Gram-negative bacteremia were reduced in the pegylated liposomal doxorubicin arm (P=0.04 and P=0.02, respectively). There was a trend towards fewer cardiac events among the patients who received pegylated liposomal doxorubicin (1/29 *versus* 6/31). The complete remission rate was 82% and, with a median follow-up of 4 years, median event-free survival and overall survival were 9 and 10 months, respectively. Despite the better tolerance of pegylated liposomal doxorubicin, no differences in survival were observed between the two arms, due to trends towards more induction refractoriness (17 *versus* 3%, P=0.10) and a higher cumulative incidence of relapse (52% *versus* 32% at 2 years, P=0.20) in the pegylated liposomal doxorubicin arm.

Conclusions

With the drug schedules used in this study, pegylated liposomal doxorubicin did not improve the outcome of elderly patients with acute lymphoblastic leukemia despite reduced toxicities. (*ClinicalTrials.gov Identifier: NCT00600977*).

Key words: elderly, acute lymphoblastic leukemia, pegylated liposomal doxorubicin, continuous infusion.

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Introduction

Data on older patients with acute lymphoblastic leukemia (ALL) are relatively scarce because of the low incidence of this disease among older adults.[1] The clinical benefit of intensive chemotherapy over best supportive care has been established in this population.[2] However, the optimal chemotherapy remains to be determined. A review of published data on 679 elderly patients in 19 studies found that the complete remission rate in this population was 59% (range, 31-85%), which is much lower than the 85-90% observed in younger adults.[3] This lower complete remission rate can be explained by both increased early mortality (23%; range, 7.5-50%) and increased induction failure (17%; range, 7-40%). The median overall survival in elderly patients with ALL, ranging from 1 to 14 months, and the estimated 2-year overall survival, ranging from 15 to 19%, are both largely inferior to those observed in younger adults. Age-adapted protocols, based on those used in younger adults but with some drugs being omitted or doses being reduced, decrease early mortality,[4] but overall survival remains poor.

New drugs or modalities of administration are, therefore, needed. The addition of anthracyclines to the vincristine-prednisone-L-asparaginase induction regimen increased the complete remission rate from 47% to 83% in adults with ALL[5] but the tolerance of such regimens in older patients is decreased. A drug administered by continuous infusion (CI) may have enhanced therapeutic effects because of increased efficacy and decreased toxicity.[6] CI anthracycline produced more rapid cytoreduction than bolus infusion in ALL[12] without significantly changing the drug's concentration within leukemic cells.[13] In the VAD regimen, developed at the MD Anderson Center, CI anthracycline seems to improve the survival of elderly patients with ALL[7] and is nowadays considered as one of the reference treatments for this population. The absence of high peak plasma concentrations of doxorubicin when this regimen is used explains the relatively low incidence of side effects,[8,9] especially cardiomyopathy, in patients with solid tumors[10] or multiple myeloma.[11] In ALL, cardiac dysfunction in children was reduced with CI doxorubicin (0/18 cases *versus* 4/18 cases after CI and bolus doxorubicin, respectively).[12] Encapsulation of anthracyclines in polyethylene-glycol liposomes might also increase the therapeutic effects of these drugs. Pegylated liposomal doxorubicin (Peg-Dox) has several pharmacological and safety advantages over conventional doxorubicin, including: (i) a much longer circulation time with a half-life of 55 hours, compared with 10 minutes for the free drug; (ii) increased extravasation through abnormal angiogenic vessels, thereby increasing the exposure of the tumor to the drug; and (iii) a significantly lower risk of cardiotoxicity, gastrointestinal side effects, myelosuppression, and alopecia.[14-17]

To evaluate the respective values of Peg-Dox and CI-doxorubicin (CI-Dox), we designed a randomized phase II trial comparing CI-Dox administered at a dose of 12 mg/m^2/day for 4 days and Peg-Dox 40 mg/m^2 during first-line treatment in elderly patients with ALL.

Design and Methods

Patients

Between March 2002 and October 2006, 60 untreated patients aged 55 years or more with non-Burkitt's, Philadelphia chromosome-negative or *BCR-ABL*-negative ALL were enrolled, from 26 centers, into the GRAALL-SA1 study. Patients with severe arrhythmia, coronary artery disease, acute heart failure, left ventricular ejection fraction less than 50%, renal or liver dysfunction, positivity for human immunodeficiency virus, or psychiatric disease were not included. Diagnostic lumbar puncture and bone marrow morphology, immunophenotyping, cytogenetics and *BCR-ABL* molecular testing were performed in all patients. In accordance with the Declaration of Helsinki, the study was approved by the ethics committee (ID 2001/22) and all patients provided written informed consent.

Treatments

Before randomization, patients received a 7-day pre-phase treatment with oral prednisone (40 mg/m^2/day) and an intrathecal injection (Figure 1). At the end of this pre-phase, corticosteroid sensitivity (defined as <1×10^9/L peripheral blood blasts) was assessed. Patients diagnosed with Philadelphia chromosome-positive and/or *BCR-ABL*-positive ALL entered another specific study while Philadelphia chromosome-negative patients were randomized between CI-Dox over 96 h or Peg-Dox. The induction chemotherapy was derived from the VAD/CVAD program[7,18] including CI-Dox 12 mg/m^2/day and CI vincristine 0.4 mg/day, both administered on days 1 to 4. Patients treated in the Peg-Dox arm received Caelyx® (Schering-Plough Corporation, Kenilworth, NJ, USA), also known as Doxil® (Ortho Biotech, Bridgewater, NJ, USA) (40 mg/m^2), infused over 1 hour on day 1. In these patients, 2 mg vincristine was infused over 5 min on day 1. All patients received oral dexamethasone (40 mg/day on days 1-4, 9-12, and 17-20). A second identical cycle with the addition of cyclophosphamide 1 g/m^2 on day 1 was started on day 29, without bone marrow assessment and whatever the blood counts. Granulocyte colony-stimulating factor (lenograstim 150 μ/m^2) was administered daily as soon as the granulocyte count dropped below 0.5×10^9/L and until it reached 1×10^9/L for 3 consecutive days. The induction response was evaluated after hematologic recovery following the second cycle. Consolidation was based on four cycles of alternating chemotherapy given 4 weeks apart. Cycles 1 and 3 comprised 2 mg intravenous vincristine on days 1, 8, and 15 in both treatment arms while CI-Dox was given at a dose of 12 mg/m^2/day over 72 h and Peg-Dox at a dose of 30 mg/m^2 over 1 hour on day 1. Cycles 2 and 4 consisted of cyclophosphamide, thioguanine, and cytarabine. Maintenance therapy included 6-mercaptopurine and methotrexate for 24 months. Allogeneic stem cell transplantation was not allowed in first complete remission. Central nervous system prophylaxis was based on six additional courses of triple intrathecal therapy during induction (n=2), the first consolidation cycle (n=3), and the second consolidation cycle (n=1), followed by cranial irradiation, performed over a 2-week period prior to the onset of maintenance therapy. During maintenance, 6-mercaptopurine was discontinued for a week if the white blood cell count was below 2×10^9/L, the neutrophil count below 1×10^9/L, and the platelet count below < 125×10^9/L; conversely, doses of 6-mercaptopurine and methotrexate were increased by 25% if the white blood cell count was above 3×10^9/L. Patients with overt central nervous system involvement were given biweekly triple intrathecal therapy until clearance of leukemic cells from the cerebrospinal fluid, followed by six course of triple intrathecal therapy and cranial irradiation. Central catheters were placed in all patients during the prednisone pre-phase. Prophylaxis against infections was left to the investigators' choice.

Statistical methods

The primary endpoint was designed as a composite

efficacy/toxicity endpoint, including the rate of patients in continuous complete remission after day 140 to test for efficacy, and having received at least the first three consolidation cycles without delay in the schedule to test for toxicity. Secondary endpoints were complete remission rate, safety, cumulative incidence of relapse and failure, cumulative incidence of death in first complete remission and treatment-related death, event-free survival, and overall survival. Failure included refractoriness to induction therapy and relapses. Treatment-related deaths included induction deaths and toxic deaths in complete remission. Outcome data were updated at the date of April 1, 2009. The primary endpoint, complete remission rates and binary covariates were compared using Fisher's exact test. Parametric data were compared using the Mann-Whitney and Fisher's test for medians and means, respectively. Survival data except cumulative incidences were estimated by the Kaplan-Meier method,[19] then compared by the log-rank test,[20] with hazard ratios estimated by the Cox model.[21] By contrast, when estimating cumulative incidences we took into account competing risks using cumulative incidence curves, then compared by Gray's test, while the Fine and Gray model was used to estimate sub-distribution hazard ratios.[22,23] The following covariates entered prognostic analysis: age (65-year cut-off), gender, Eastern Cooperative Oncology Group performance status (0/1 *versus* 2/3), fever at diagnosis, serum creatinine level (100 μmol/L cut-off), serum albumin level (35 g/L cut-off), white blood cell count (30×10^9/L cut-off), platelet count (100×10^9/L cut-off), ALL lineage (B-cell precursors [BCP] *versus* T-lineage), cytogenetics (poor *versus* standard risk), corticosteroid sensitivity, and randomization arm. Factors associated with a significant impact in univariate analysis were retained for multivariate logistic regression. The type 1 error was fixed at the 5% level. All tests were two-tailed. Statistical analyses were performed with the Stata 10.0 software package (Texas Union, TX, USA).

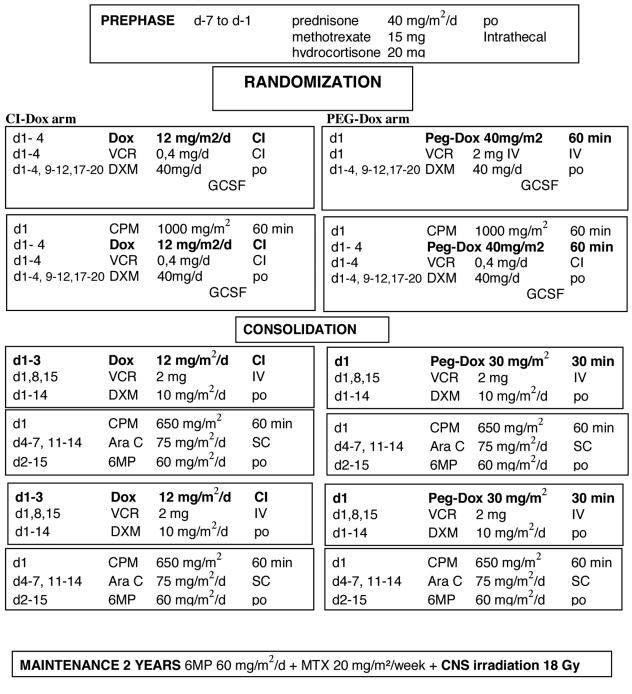

Figure 1. Treatment protocol.

Results

Patients' characteristics

Thirty-one patients were randomized to receive CI-Dox and 29 patients to receive Peg-Dox (Table 1) (Consort Flowchart: *Online Supplementary Figure S1*). The median age of all the patients was 66 years (range, 55-80 years) and 17% of patients had a white blood cell count above 30×10^9/L. Two patients had central nervous system involvement at diagnosis. Fifty-one patients had BCP-ALL and seven patients had T-ALL. Cytogenetics results were available for 48 patients of whom 16 were classified as having a poor risk: four with t(4;11), one with t(1;19), four with near-triploidy, one with hypodiploidy (44 Chr), and six with complex karyotypes with five or more unrelated abnormalities. *BCR-ABL* molecular testing was negative in patients in whom cytogenetic analysis failed. The distribution of clinical and laboratory characteristics was comparable in both randomization groups (Table 1). However, patients in the Peg-Dox group more frequently had T-ALL (6/29 *versus* 1/31, P=0.05) and a trend for more frequent corticosteroid-resistant ALL (5/29 *versus* 1/31, P=0.1).

Efficacy

After two induction courses, the overall complete remission rate was 82% (49 patients); five patients died during induction, all from invasive fungal infections, and six patients failed to achieve complete remission. Salvage ther-

Table 1. Patients' characteristics.

	CI-Dox	Peg-Dox
Patients (n)	31	29
Median age, years (range)	68 (55-77)	66 (60-80)
Sex (male/female)	18/13	14/15
ECOG performance status (0/1/2/3)	11/13/5/2	8/13/8/0
Prior history of cancer (n)	3	4
Prior cardiac disease (n)	8	4
Central nervous system involvement (n)	1	1
Fever at diagnosis (n)	10	9
Median WBC$\times10^9$/L (range)	4.2 (0.9-459)	6.7 (1-309)
WBC > 30×10^9/L (n)	5	5
Median hemoglobin level g/L (range)	96 (66-152)	101 (41-155)
Median platelet count $\times10^9$/L (range)	63 (21-185)	79 (18-309)
Median serum albumin g/L (range)	34 (24-50)	36 (3-45)
Median serum fibrinogen g/L (range)	4.6 (1.9-7.2)	4.0 (0.7-7.0)
Median serum creatinine mmol/L (range)	83 (43-140)	80 (44-147)
Lactate dehydrogenase level >1.25 N (%)	64	44
Aspartate aminotransferase level >1.25 N (%)	44	25
Alanine aminotransferase level >1.25 N (%)	34	36
Alkaline phosphatase level >1.25 N (%)	32	28
Immunophenotype BCP/T/BAL (n)*	29/1/1	22/6/1
Pro-B/ common B/ PreB, Pro-T/cortical T, NS	4/14/8, 1/0, 2	3/12/8, 2/4, 0
Cytogenetics (standard/poor/failure) (n)	17/8/6	15/8/6
Median prephase duration days ± SD	8.9±2.9	9.2±1.9
Corticosteroid resistance (n) **	1	5

**P= 0.05; **P=0.1; ECOG: Eastern Cooperative Oncology Group; WBC: white blood cell count; BCP: B-cell precursor; BAL: biphenotypic acute leukemia; NS not specified because of incomplete immunophenotype; n: number; N: normal.*

apy was left to the investigators' decisions. One patient in whom Peg-Dox failed was successfully rescued by administration of the CI-Dox regimen. The complete remission rate was lower in the Peg-Dox arm (72% *versus* 90%, *P*=0.10), due to a higher proportion of patients alive with refractory ALL after induction (17% *versus* 3%, *P*=0.10) (Table 2). With respect to the primary endpoint, i.e. the rate of patients alive in continuous complete remission after day 140 who had received at least the first three consolidation cycles, no difference was found between the two randomization arms: 48% in the Peg-Dox arm (14 patients) *versus* 39% in the CI-Dox arm (12 patients) (*P*=0.60). At 2 years, the overall cumulative incidence of relapse was 41% (95% confidence interval, 29-56%). The 2-year cumulative incidence of relapse in the Peg-Dox arm was 52% (95% confidence interval, 33-74%) whereas in the CI-Dox arm it was 32% (95% confidence interval, 18-53%; *P*=0.20). The 2-year cumulative incidence of failure (including complete remission achievement, failure and relapse) was higher after Peg-Dox than after CI-Dox, but without the difference reaching statistical significance (55% [95% confidence interval, 38-73%] *versus* 32% [95% confidence interval 19-52%]; *P*=0.12). As described below, this trend towards a lower anti-leukemic efficacy observed in the Peg-Dox arm was balanced by lower toxicity. Cumulative incidences of treatment-related death and death in first complete remission were higher in the CI-Dox arm, even if the differences were not statistically significant (*P*=0.35 and *P*=0.32, respectively) (Table 2). With a median follow-up of 4 years, median event-free survival and overall survival were 9 and 10 months, respectively, for the entire population. At 2 years, the event-free and overall survival rates were both estimated at 24% (95% confidence interval, 11-41%) in the Peg-Dox arm *versus* 35% (95% confidence interval, 19-52%) in the CI-Dox arm (*P*=0.41 and P=0.47 for event-free survival and overall survival, respectively, by the log-rank test) (Figures 2 and 3) confirming that survival was very short in these patients after complete remission induction failure or relapse.

Prognostic factors

A prognostic analysis was performed for complete remission achievement and overall survival. In univariate analysis, only age (complete remission rate, 100% if age < 65 years *versus* 69% if age ≥ 65 years; *P*=0.002), BCP-ALL (complete remission rate, 88% if BCP-ALL *versus* 29% if T-ALL; *P*=0.002), and corticosteroid-sensitivity (complete remission rate, 87% if corticosteroid sensitive *versus* 33% if corticosteroid-resistant; *P*=0.008) were clearly predictive of achievement of complete remission. In multivariate analysis, only age 65 years or over and T-cell lineage predicted failure to achieve complete remission (*P*=0.005 and *P*=0.03, respectively). Age 65 years or over was the only factor that significantly influenced overall survival (2-year overall survival, 46% [95% confidence interval, 26-64%] in younger patients *versus* 19% [95% confidence interval, 9-34%] in older patients; *P*=0.05). Seven patients had a personal history of cancer but this was not of particular prognostic significance.

Safety

The main non-hematopoietic treatment-related adverse events are listed in Table 3. Overall, patients treated in the Peg-Dox arm experienced fewer infectious and cardiac events than patients in the CI-Dox arm. During induction, grade 3/4 infections were observed in 48% of induction cycles in the CI-Dox group and in 29% of cycles in the Peg-Dox group (*P*=0.04). During consolidation, grade 3/4 infections were observed in 18% of courses in the CI-Dox group and in 8% of courses in the Peg-Dox group (*P*=0.10). Invasive fungal infections, including pulmonary invasive aspergillosis or candidemia, occurred in 11 patients, only during the induction phase, with 45% of these infections being fatal (5 patients). While cases of bacteremia due to Gram-positive cocci were equally distributed between the two randomization groups, cases of Gram-negative bacteremia were more frequent in the CI-Dox group, during both the induction (9 cases *versus* 1 case, *P*=0.02) and the consolidation phases (7 cases *versus* 2 cases, *P*=0.09) (Table 3).

Table 2. Treatment results.

	CI-Dox	Peg-Dox	*P* value
Patients (n)	31	29	-
Median follow-up for surviving patients (years)	4.1	4.3	
Complete remission rate after two induction cycles, n (%)	28 (90%)	21 (72%)	0.10
Refractory acute lymphocytic leukemia after induction, n (%)	1 (3%)	5 (17%)	0.10
Induction death, n (%)	2 (7%)	3 (10%)	0.67
Patients alive at day 140 having received at least the first three consolidation cycles, n (%) *	12 (39%)	14 (48%)	0.60
Relapse, n	14	14	-
Death in first complete remission, n	9	4	-
Cumulative incidence of relapse at 2 years (95% confidence interval)	32% (18-53)	52% (33-74)	0.20
Cumulative incidence of failure at 2 years (95% confidence interval)**	32% (19-52)	55% (38-73)	0.12
Cumulative incidence of death in first complete remission at 2 years (95% confidence interval)	37% (20-60)	19% (6-50)	0.32
Cumulative incidence of treatment-related death at 2 years (95% confidence interval)***	32% (19-52)	21% (10-40)	0.35
Event-free survival at 2 years (95% confidence interval)	35% (19-52)	24% (11-41)	0.41
Overall survival at 2 years (95% confidence interval)	35% (19-52)	24% (11-41)	0.47

*CR: complete remission; *primary endpoint; **Cumulative incidence of failure was estimated in the entire population including refractoriness to induction and relapse as events, while induction deaths and deaths in first CR accounted as competing events; ***Cumulative Incidence of treatment-related death was estimated in the entire population of patients including induction deaths and post-CR treatment-related deaths as events, while refractoriness to induction, relapses, or deaths unrelated to ALL therapy were considered as competing events.*

Hematologic toxicity was moderate and reduced in the Peg-Dox arm (Table 4). During induction neutrophil, erythroid, and megakaryocytic toxicities were reduced in the Peg-Dox arm, while during consolidation only erythroid and megakaryocytic toxicities were significantly reduced in the Peg-Dox arm.

With respect to cardiac toxicity, 12 patients had a history of cardiovascular disease before inclusion in the study (8 cases of arterial hypertension and 4 cases of myocardial infarction). Nevertheless all of them had a normal left ven-

Table 3. Non-hematologic adverse events.

	CI-Dox	Peg-Dox
Infections during induction phase		
Overall incidence of grade 3/4 infections, n (% of courses) *	29/60 (48%)	16/55 (28%)
Invasive fungal infection, n	7	4
Pulmonary aspergillosis/zygomyces	5	3
Candidemia	2	1
Fatal invasive fungal infection: candidemia/aspergillosis	1/1	1/2
Gram-positive cocci bacteremia, n	10	9
Gran-negative bacilli bacteremia, n *	9	1
Clostridium difficile colitis, n	2	1
Pneumonia/septic shock, n	1	1
Infections during consolidation phase		
Overall incidence of grade 3/4 infections, n (% of courses)	14/78 (18%)	7/82 (8%)
Invasive fungal infection, n	0	0
Gran-positive bacteremia, n	3	3
Gran-negative bacteremia, n	7	2
Clostridium difficile colitis, n	1	0
Pneumonia/septic shock, n	2	2
Other events		
Cardiac events ##	6	1
Induction therapy-related diabetes	5	4
Induction therapy-related severe constipation	1	2
Peripheral neuropathy	0	3
Deep venous thrombosis	4	3
Pneumocystis carinii infection	1	1
EBV-related lymphoproliferative syndrome	1	0
BK virus urinary tract infection	1	0
Treatment-related deaths		
Induction death, n (%)	2 (7%)	3 (10%)
Post-remission treatment-related death, n	8/28 (28%)	3/21 (14%)
All treatment-related death, n	10 (32%)	6 (21%)

*##including four atrial fibrillations, two myocardial infarctions, and one left ventricular dysfunction (P = 0.12 between both arms); *P < 0.05.*

Table 4. Hematologic toxicities.

	CI-Dox mean (SD)	Peg-Dox mean (SD)	*P* value Mean Comparison (Student)	CI-Dox median (95%CI)	Peg-Dox median (95%CI)	*P* value median comparaison (Mann Whitney)
During Induction						
Neutrophils <0.5×10⁹/L (days)	12.7 (9.7)	7.8 (7.3)	0.046	10.5 (4.5 - 18)	6.5 (2 - 10)	0.08
Neutropenia nadir	0.17 (0.2)	0.50 (0.95)	0.11	0.1 (0.03 - 0.29)	0.20 (0.07 - 0.32)	0.2
G-CSF infusion (days)	12.4 (8.1)	10.6 (8.2)	0.42	11 (6.6 - 17)	9 (6 - 14.4)	0.5
RBC units transfused	8.7 (6.8)	5.4 (4.6)	0.04	6 (4 - 10)	4 (2 - 81)	0.03
Thrombocytopenia <50×10⁹/L (days)	15.7 (13.6)	7.9 (11.5)	0.03	14 (9 - 22)	1 (0 - 13)	0.01
During consolidation cycles						
Neutrophils <0.5×10⁹/L (days)	1.78 (3.8)	2.6 (5.1)	0.21	0 (0 - 0)	0 (0 - 0)	0.6
RBC units transfused	2.9 (4.3)	1.14 (1.7)	0.003	2 (0.5 - 2))	0 (0 - 2)	0.005
Thrombocytopenia <50×10⁹/L (days)	3.64 (7.25)	2.81 (5.8)	0.02	0 (0 - 0.04)	0 (0 - 0)	0.9

G-CSF: granulocyte colony-stimulating factor; RBC: red blood cells.

tricular ejection fraction. None of the patients received cardio-protective agents such as dexrazoxane during therapy. Seven patients experienced a cardiac event during the treatment, all but one of whom were in the CI-Dox group (P=0.12). These events included four cases of atrial fibrillation (2 during induction including the only cardiac event in the Peg-Dox arm and 2 during consolidation), one case of asymptomatic impairment of left ventricular ejection fraction occurring at the end of consolidation, and two late myocardial infarctions, 6 and 30 months after the beginning of maintenance therapy. The occurrence of cardiac complications was similar in patients with or without a history of cardiac disease (2/12 *versus* 5/43, P=NS)

Overall, five patients died from induction toxicity (all from an invasive fungal infection) and 13 patients died in first complete remission, including 11 from post-complete remission treatment toxicity (1 patient in each arm later died from recurrence of a previous cancer). In the CI-Dox arm, two patients died from induction toxicity, and eight patients died from post-complete remission treatment toxicity (including 5 with infections). In the Peg-Dox arm, three patients died from induction toxicity, and three patients died from post-complete remission treatment toxicity (including two with infections).

Discussion

The GRAALL-SA1 study is the largest randomized study of patients over 60 years old with ALL ever published. The few fully published studies with more patients consisted of reports of several different chemotherapy regimens.[4,24] This emphasizes the difficulty in obtaining a significant improvement in this rare and very poor-risk population. In the GRAALL-SA1 study at the drug schedules used, Peg-Dox was associated with lower toxicity but did not improve survival due to a higher rate of induction failure and a higher cumulative incidence of relapse.

In this population of elderly patients with ALL, liposomal encapsulation decreased the overall toxicity of doxorubicin, especially in terms of myelosuppression, infections, and cardiotoxicity. The difference in the incidences of severe infection between the two arms appeared to result from less toxicity in patients treated with Peg-Dox as the incidence in the CI-Dox arm was similar to that in previous studies.[10,19,20] The high incidence of Gram-negative bacteremia observed after CI-Dox treatment is reminiscent of our previous results with CI daunorubicin in younger ALL patients.[25] This is likely related to the CI doxorubicin, rather than to the CI vincristine, as it was also observed during the consolidation phases that included a standard 5-minute vincristine infusion. The use of dexamethasone in both arms might also have increased the rate of infections, especially invasive fungal infections.[26] Studies evaluating systematic prophylaxis of Gram-negative and fungal infections would be useful. Hematologic toxicity was significantly decreased after Peg-Dox for all three bone marrow lineages. Cardiac tolerance also seemed to be better with Peg-Dox than with CI-Dox. The prevalence of doxorubicin-related cardiac complications is not specifically described in the literature for older patients, but chronic heart failure seems to occur more frequently and at lower cumulative doses.[27] There are reports of the occurrence of chronic heart failure after a cumulative doxorubicin dose of less than 200 mg/m^2.[24,25] Finally, although the difference was not statistically significant, treatment-related mortality and post-remission treatment-related mortality were slightly reduced in the Peg-Dox arm.

Despite reduced toxicity, the Peg-Dox regimen was not associated with improved survival. The complete remission rates observed (90% with CI-Dox, 72% with Peg-Dox) were higher than those previously reported,[3] with for instance a complete remission rate of only 58% in the VAD study from the MD Andersen Center.[7] This might be related to the extensive use of granulocyte colony-stimulating factor during the induction phase[28] and the absence of patients with Philadelphia chromosome-positive ALL in our study. In any case, more induction failures (17% *versus* 3%) and more relapses (52% *versus* 32%) were observed in the Peg-Dox arm with only 32% of patients being failure-free at 2 years *versus* 55% in the CI-Dox arm (P=0.12). The present 17% induction failure and 10% induction death rates in the Peg-Dox arm are not in line with the results of a small study on the use of liposomal daunorubicin in 15 patients, in whom the rate of patients alive in failure after induction was only 7%, with 20% induction deaths.[29]

Overall, our results are disappointing. They may have

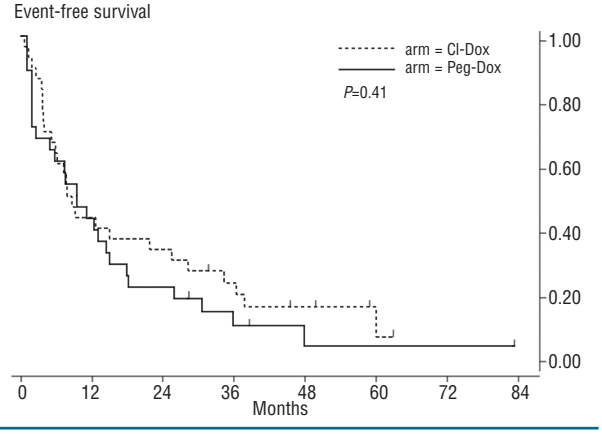

Figure 2. Event-free survival according to randomization arm.

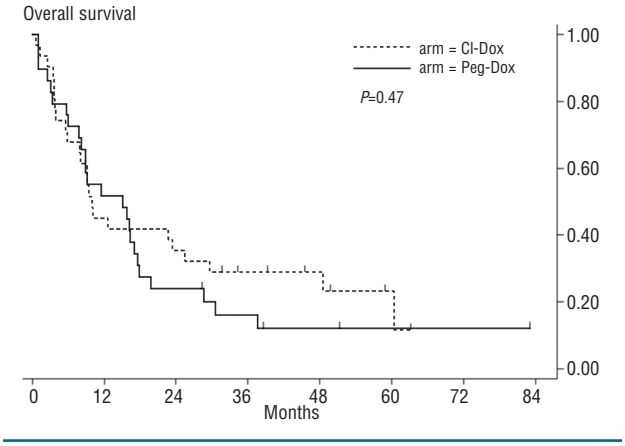

Figure 3. Overall survival according to randomization arm.

been due in part to the slight imbalance in favor of more T-ALL in the Peg-Dox arm, although this feature was not identified as a poor prognostic indicator in previous studies of ALL patients over 60 years old.[1,2,4,7,24,28,30-40] Another explanation may be an incorrect calculation of the Peg-Dox dose equivalence. As no pharmacokinetic studies were available comparing CI-Dox to Peg-Dox, the Peg-Dox dose was defined according to the pivotal randomized study in metastatic breast cancer[15] and studies performed in high-grade non-Hodgkin's lymphoma[41,42] which applied a 1.2 dose reduction factor between conventional doxorubicin and Peg-Dox, the total conventional doxorubicin dose being divided over 4 days in the CI arm. More recent studies have utilized almost identical dosages of CI-Dox and Peg-Dox.[43,44] Indeed, in multiple myeloma, overall survival and progression-free survival rates were similar with CI-Dox 9 mg/m^2/day for 4 days or Peg-Dox 40 mg/m^2.[43] A similar misinterpretation was noted with the dose of *E-Coli*-derived L-asparaginase and *Erwinia*-derived L-asparaginase, the supposed low toxicity being the reflection of lower biological activity and, therefore, efficacy.[44] An effect of the two different ways of vincristine administration can reasonably be ruled out because vincristine causes little or no hematologic or cardiac toxicity. Moreover, the vincristine bolus infusion is probably not responsible for the lower efficacy of the "bolus" arm as this is the usual method of administration.

Although the major weakness of this study is the lack of sufficient power to detect small differences due to the rarity of the disease and low number of patients, the safety findings provide us with many important points for investigating ALL in the elderly. Because CI-Dox has not been unequivocally demonstrated to be better than standard doxorubicin, a randomized study between standard bolus doxorubicin *versus* CI-Dox *versus* Peg-Dox associated with pharmacokinetic studies should be encouraged, probably in younger patients, but with clear stopping rules as there is a real possibility that Peg-Dox might be inferior to standard doxorubicin.

Appendix

The following centers and investigators participated in the GRAALL-SA1 trial: France: Aix en Provence – Cailleres, Da Silva; Amiens –Vaida, Royer, Dubus, Capiod, Marolleau; Angers – Francois, Hunault, Ifrah, Moles, Guardiola, Marie, Genevieve, Baranger, Chassevent, Blanchet; Avignon – Boulat, Derre; Besançon – Brion, Deconninck, Garnache, Larosa Ottou, Ferrand; Bordeaux –Leguay, Pigneux, Milpied, Perry, Lacombe, Tabrizi, Lippert, Guerin, Foucaud; Caen – Reman, Lepesant, Salaun, Plessis, Naguib, Leporrier; Colmar – Audhuy, Raby, Bauly, Moskochenko; Grenoble – Garban, Bulabois, Gressin, Rolland, Jacob, Lefebvre, Leroux, Callanan, Cahn; Limoges – Turlure, Bordessoule, Chaury, Trimoreau, Gachard; Lyon – Le, Nicolini, Tavernier, Thiebaut, Thomas, Lheritier, Girard, Wattel, Tigaud, Hayette, Michallet; Marseille –Lafage-Pochitaloff, Montpellier – Fegueux, Quittet, Grosjean, Taib, Taviaux, Dupont, Rossi; Mulhouse – Arkam, Ojeda Uribe, Iglarz, Drenou, Jeandidier, Isaac; Nancy – Witz, Ranta, Bologna, Lesesve, Witz, Gregoire, Bene; Nantes – Chevallier, Delaunay, Moreau, Harousseau, Saulquin, Garand, Talmant, Avet-Loiseau; Nice – Gratecos, Legros, Sirvent, Touitou, Ticchioni, Raynaud; Paris-Hotel Dieu – Legrand, Rio, Marjanovic, Vekhoff, Lacombe, Perot, Ramond, Viguie, Tang, Marie; Paris Necker – Buzyn, Couderc, Asnafi, Valensi, Radford-Weiss, Macintyre, Varet; Paris Pitié-Salpétrière – Dhedin, Aliammar, Merle-Beral, Nguyen-Khac, Davi, Leblond, Vernant; Paris Saint-Louis – Raffoux, Treilhou, Maarek, Daniel, Soulier, Cayuela, Miclea, de Labarthe, Dombret; Reims – Himberlin, Baury, Daliphard, Luquet, Cornillet-Lefebvre, Delmer; Rennes – Escoffre-Barbe, Lamy, Picouleau, Roussel, Henry, Ly Sunnaram, Fest; Strasbourg – Bilger, Fohrer, Lioure, Ame, Eischen, Leymarie, Gervais, Herbrecht; Toulouse – Huguet, Recher, Daniel, Kuhlein, Dastugue, Demas, Delabesse, Attal,; Versailles – Choquet, Rousselot, Taksin, Pousset, Terre, Castaigne; Belgium: Jolimont – Delannoy, Tacal, Rack.

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