Adding lomustine to idarubicin and cytarabine for induction chemotherapy in older patients with acute myeloid leukemia: the BGMT 95 trial results

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ABSTRACT

Background and Objectives

Treatment of acute myeloid leukemia (AML) in older patients remains unsatisfactory. The BGMT 95 trial for older patients set out to improve the outcome of these patients by adding a third drug (lomustine) to a 5+7 idarubicin and cytarabine schedule at induction and evaluating intermediate-dose cytarabine as consolidation.

Design and Methods

A multicenter randomized trial was performed comparing induction therapy with idarubicin and cytarabine, 5+7 (IC) to induction therapy with the same drugs plus lomustine (CCNU), 200 mg\m^2 orally on day 1 (ICL). Patients in complete remission (CR) were then randomized to receive either maintenance therapy or intensification with intermediate-dose cytarabine and idarubicin followed by maintenance therapy.

Results

Between 1995 and 2001, 364 patients (≥60 years) from ten centers were included. The CR rate was 58% for patients in the IC arm and 67% for patients in the ICL arm (p=0.104). The median overall survival (OS) was 7 and 12 months respectively (p=0.05), but OS at 2 years was not statistically different: 31±7% for patients in the ICL arm vs 24±6% for those in the IC arm. The two post-remission strategies yielded similar results.

Interpretation and Conclusions

Adding lomustine to induction with idarubicin and cytarabine therapy did not statistically improve survival in elderly patients with AML. Adding intermediate-dose cytarabine to consolidation therapy did not improve outcome.

Key words: AML, older patients, lomustine.

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The incidence of acute myeloid leukemia (AML) increases with age, with more than 50% of cases diagnosed over 60 years of age and a median age at diagnosis of almost 65 years.[1] Unfortunately, progress in the therapy of AML has been mainly restricted to younger patients. Treatment in older patients remains unsatisfactory, with a complete remission (CR) rate around 50% after conventional anthracycline and cytarabine regimens, a relapse risk for remitters around 80% and a 3-year survival of 10 to 20%.[2-7] The outcome of older patients is worse than that of younger patients for several reasons. Biologically, an adverse karyotype (abnormalities or partial losses of chromosomes 5 and 7 or complex chromosomal aberrations) or a chemoresistant phenotype (greater proportion of patients with high expression of multidrug resistance glycoprotein MDR1) and pre-existing or underlying myelodysplasia are frequent.[4,8-11] Clinically, older patients are less able to withstand intensive chemotherapy such as high-dose cytarabine or hematopoietic stem cell transplant for reasons of comorbidity.[1,10,12] There is, therefore, a need to improve outcomes by developing new programs. For example, during induction chemotherapy a third drug could be added to the association of cytarabine and anthracycline.

For this purpose, lomustine (CCNU), a nitrosourea with anti-leukemic activity[13-15] was used in previous studies in which prolonged CR and improved survival were shown.[16,17] However, these studies required confirmation as they concerned younger populations of patients and were not controlled. Moreover, the outcome of older patients could be improved by using high-dose chemotherapy for consolidation, such as intermediate-dose cytarabine. Two large, randomized studies comparing high-dose cytarabine to lower doses of this agent showed that an intensified approach results in improved disease-free survival (DFS) and overall survival (OS). However, the benefit on DFS and OS of high-dose cytarabine administered after remission was demonstrated only in patients 60 years of age or younger.[18,19]

The BGMT 95 trial for older patients set out to improve the outcome of these patients by testing the two options described above by adding a third drug (lomustine) to a 5 + 7 idarubicin and cytarabine schedule at induction and evaluating intermediate-dose cytarabine as consolidation.

Design and Methods

Patients

Between July 1995 and April 2001, 364 patients were included in the BGMT 95 trial from ten centers in southern France. Patients aged 60 years and older with *de novo* AML according to French-American-British (FAB) criteria[20] were eligible. Since June 1999 the rate of 20% of myeloblasts was used according to the WHO classification.[21] Patients with myeloproliferative syndromes prior to the diagnosis of AML, those who previously had myelodysplastic syndrome (diagnosed from blood and marrow abnormalities) for a minimum period of 3 months and patients pretreated with chemo- or radiotherapy were excluded. Patients with acute promyelocytic leukemia were not eligible for this study. Eligibility criteria also included normal cardiac function with left ventricular ejection fraction ≥50%, absence of unstable cardiac arrhythmia or unstable angina, as well as unimpaired renal function (creatinine <180 μmol/L) and liver function (bilirubin <35 μmol/L) functions. Patients in poor condition prior to initiation of therapy (i.e. ECOG performance status 3 or 4) were not included. Institutional ethical review committee approval was obtained and informed consent from the patients was required.

Treatment

The design of the study is illustrated in Figure 1.[7]

Induction therapy: patients were randomized to receive idarubicin plus cytarabine (IC) or the same drugs plus lomustine (ICL), the latter given at the dose of 200 mg/m^2 orally on day 1. Patients with persistent leukemia in the bone marrow, defined by at least 20% marrow cellularity with more than 5% blasts on day 14 or at a subsequent time point following initiation of induction therapy, received a second course of induction chemotherapy identical to the initial induction course. Non-responders to the second induction course were taken off the protocol.

Consolidation therapy: after completing induction treatment, patients who were in CR after one or two induction courses received a course of consolidation (IC') therapy with idarubicin and subcutaneous cytarabine. Subsequently, if stable remission persisted, the patients received maintenance therapy or maintenance therapy preceded by a second consolidation (IIC) with intermediate-dose cytarabine. Randomization was performed as soon as CR was achieved.

Maintenance therapy: this was given to all patients with persisting CR 1 month after completing the first (IC') or second (IIC) consolidation and consisted of the following: five courses of combination chemotherapy 1, 3, 6, 9 and 13 months after the last consolidation, namely cytarabine (subcutaneously) and idarubicin and between these courses for 1 year: a continuous regimen of methotrexate and 6-mercaptopurine, as alternating 10-day courses.[7]

Supportive care: for granulocytopenic patients, supportive care consisted of reverse isolation in a single-bedroom, treatment with oral non-absorbable antibiotics and oral amphotericin B (according to the protocol of each participating center) and sterilized food. Patients who developed fever were treated empirically with par-

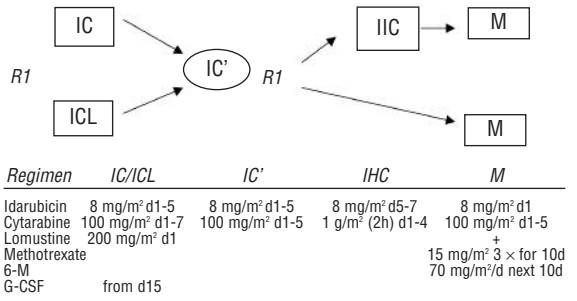


Figure 1. Study design. IC: idarubicin and cytarabine; ICL: idarubicin, cytarabine and lomustine; IIC: idarubicin and intermediate-dose cytarabine; M: maintenance. R1 and R2: successive randomization; 6-M: 6-mercaptopurine; G-CSF: granulocyte colony-stimulating factor.

enteral broad spectrum antipseudomonal antibiotics. Antibiotics were continued until the absolute neutrophil count (ANC) was over 0.5×10^9/L and clinical signs of infection had resolved. Single donor platelet transfusions were administered to maintain the platelet count above 20×10^9/L. Red blood cells were transfused to maintain the hemoglobin level above 8 g/dL. Lenograstim (Chugaï), at the dose of 263 μg/day was administered systematically (to reduce the period of neutropenia) once daily from day 15 after starting induction and the eventual second consolidation until the ANC reached 0.5×10^9/L for 3 consecutive days.

Definitions and end-points

Chromosomal analysis of bone marrow was performed at diagnosis. Analyses were conducted in five out of the ten centers and referred by the others to these centers. Data were then reviewed by the BGMT cytogenetics committee. Cytogenetic results are described according to the International System for Human Cytogenetic Nomenclature (ISCN.)[22] Three prognostic groups were defined: (i) *low risk*: patients with t(8;21)(q22;q22) or inv(16)(p13q22); (ii) *high risk*: patients with complex abnormalities (≥3), del(5q),-5, -7, 3q rearrangements, t(9;22), t(6;9), or 11q23 rearrangements; (iii) *intermediate risk:* patients with any other karyotypes. Given the small number of patients with favorable cytogenetics (n=14), these patients were combined with the intermediate cytogenetic risk group for analyses. Toxicities were defined and graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 2.0. The duration of neutropenia and thrombocytopenia was defined as the time (in days) from the start of chemotherapy to the day of ANC recovery to more than 1×10^9/L and to platelet recovery to more than 20×10^9/L, respectively. CR was defined as a normocellular bone marrow aspirate containing <5% leukemic blast cells and showing evidence of normal maturation of other bone marrow elements with a normal peripheral blood count (neutrophils 1×10^9/L and platelets 100×10^9/L) and disappearance of any clinical signs of the disease.

Drug-resistant disease was defined as follows: appropriately treated patients who survived at least 7 days after completion of the final dose of the initial course of treatment but whose last post-treatment peripheral blood smear and/or bone marrow sample showed persistent AML; patients in whom marrow hypocellularity was achieved but in whom leukemic cells grew again within 4 weeks after the end of a course of induction therapy; and patients who died ≥36 days after induction without achieving remission.

Induction death included early death, i.e. death during the 7 days following the end of a course of induction therapy. Hypoplastic death was defined as death during a period of severe marrow hypoplasia <36 days after the end of a course of remission induction therapy.

Statistical methods

The primary objective of this study was to assess the ability of lomustine to increase the CR rate and to improve OS. The secondary objective was to test the effect of intermediate-dose cytarabine on survival, and to analyze the impact of prognostic factors on CR and survival. The sample size of the whole study was based on the primary objective. According to the BGMT database for AML in the elderly, the CR rate with conventional chemotherapy was 60% and the 2-year survival rate was about 20%. To detect an increase of 15% in CR and 20% in 2 year-survival with a power of 90% and type I error of 5%, a total of 350 patients needed to be randomized. Randomization was centralized and balanced within each center. Comparisons of treatment outcomes between arms were based on intent-to-treat analyses of all eligible patients. As the analysis of the outcome after second randomization showed no differences between groups, patients were analyzed together for the response to the first randomization. The two-tailed Fisher's exact test[23] was used to compare categorical data (e.g. CR rates). Continuous parameters (e.g. non-hematologic toxicity) were compared using the Mann-Whitney non-parametric test. Univariate and multivariate logistic regression analyses were used to assess factors associated with the response. OS was measured from the date of the first randomization to the date of death. Event-free survival (EFS) was measured from the date of the first randomization until progression of the disease or death, regardless of cause. Patients still alive without progression at the time of the analysis were censored at the last follow-up. DFS was measured from the date of first CR until the date of the the first event from any cause with observation censored at the date of last contact for patients last known to be alive without a report of relapse or death in CR. The cumulative incidence of relapse was estimated from the date of entering CR to the date of relapse considering death without relapse as a compet-

Table 1. Characteristics of the 364 eligible patients by induction arm.

	IC group	ICL group	p
Number of patients	186	178	
Median age, years (range)	68 (60-83)	69 (60-84)	NS
Sex ratio, male/female	1.07	1.25	NS
FAB subtype			NS
M0	20	18	
M1	50	46	
M2	54	43	
M4	27	30	
M5	26	20	
M6	8	18	
M7	1	3	
Performance status (WHO)			NS
0	34	40	
1	98	99	
2	52	36	
Median WBC count ($\times 10^9$/L)	7.4	7.15	NS
(range)	(0.6-250)	(0.4-300)	
WBC count $<30\times10^9$/L	150	126	NS
WBC count $\geq30\times10^9$/L	36	52	0.04
Median marrow blast percentage	62	65	
(range)	(24-100)	(20-100)	NS
Median blood blast percentage	24	28	
(range)	(0-98)	(0-98)	NS
Median platelet count (10^9/L)	68	60	
(range)	(3-782)	(3-387)	NS
Platelet count $<50\times10^9$/L	65	80	NS
Platelet count $\geq50\times10^9$/L	120	98	NS
Cytogenetic group			NS
Not analyzed/failed analysis	35	34	NS
Favorable	7	7	NS
Intermediate	91	88	NS
Adverse	53	49	NS

ICL: idarubicin, cytarabine and lomustine; IC: idarubicin and cytarabine; FAB: French-American-British; WBC: white blood cell.

ing risk.[24] Survival curves and time to neutrophil recovery were analyzed using the Kaplan-Meier product-limit estimator.[25] The standard errors of the estimates were obtained with the Greenwood formula[26] and comparisons between groups with the log-rank test.[27] The multivariate proportional hazard regression model[28] was used to assess factors associated with OS, EFS and DFS. In the multivariate analysis, all variables significant at the level of 0.2 in the univariate analysis were considered. Our modeling strategy was based on a downward stepwise method, retaining variables that were significantly associated at $p<0.05$. All calculations were performed using SPSS for Windows (SPSS, Inc, Chicago, IL, USA). Confidence intervals (CI) were calculated at the 95% confidence level.

Results

Induction randomization

Patients' characteristics

A total of 364 patients from ten institutions were enrolled in this study between July 1995 and April 2001. Of the 364 patients, 186 were randomized to the IC arm and 178 to the ICL arm. There were no statistically significant differences in the main patients' and disease characteristics (Table 1) between the two treatment arms, except that there were more patients with hyperleukocytosis (white cell count $\geq30\times10^9$/L) in the ICL group ($p=0.04$). The median age at diagnosis was 68 and 69 years for the IC and ICL groups, respectively. Only 12 out of the 364 patients had a marrow blast count between 20 and 30% (3.2%). The cytogenetic prognostic groups were similarly distributed between the patients in the IC and ICL arms.

Table 2. Response to induction therapy.

	IC group n=186		ICL group n=178		p value
	n	%	n	%	
Complete remission	108	58	119	67	0.104
Complete remission with one course	101	54	115	65	0.055
Complete remission in favorable and intermediate cytogenetic group	63/98	64	68/95	71	0.286
Complete remission in adverse cytogenetic group	21/53	40	29/49	59	0.074
Drug-resistant disease	43	23	24	13	0.021
Induction death	35	19	35	20	NS
Early death	12	6	8	4	
Hypoplastic death	23	12	27	15	

Response to induction therapy

The CR rate was 67% in the ICL arm vs. 58% in the IC group ($p=0.104$). The proportion of CR after one course was 65% with ICL vs. 54% with IC ($p=0.055$). Among the 82 patients who did not achieve CR after a single course of induction therapy, 43 received the planned second course of induction therapy: 32/54 in the IC arm and 11/28 in the ICL arm. Seven patients out of 32 (22%) and four out of 11 (36%) achieved CR after the second course in the IC and ICL groups, respectively. Some patients were excluded from the second induction course because of poor performance status (17/22 IC and 14/17 ICL) or poor cytogenetic features (5/22 IC and 3/17 ICL). The CR rate among patients with adverse cytogenetic features who received lomustine was 29/49 (59%) vs 21/53 (40%) in those who did not, $p=0.074$. The CR rate for patients with favorable or intermediate cytogenetic features who received lomustine was 68/95 (71%) vs 63/98 (64%) in those who did not, $p=0.286$.

The incidence of induction death after the induction course was not different between the groups: 35 of the 186 (19%) IC patients vs. 35 of the 178 (20%) ICL subjects. Drug-resistant disease was significantly reduced with lomustine (13 vs. 23%, respectively; $p=0.021$) (Table 2).

Table 3. Toxicity and supportive care by treatment arm.

Fatal toxicity	*IC group n=35*	*ICL group n=35*	
Bacterial infection	5	4	
Fungal infection	3	1	
Unclassified infection	6	3	
Other pneumonia	2	2	
Acute respiratory distress syndrome	2	5	
Disseminated intravascular coagulopathy or coagulation	1	0	
Hemorrhage	3	5	
Organ failure	12	15	
Drug toxicity	1	0	
Toxicity			*p*
Liver toxicity grade 3-4	3%	10%	0.01
Median time to achieve 50×10^9/L platelets	18 (0-99)	23 (3-119)	0.001
Median time to achieve 0.5×10^9/L neutrophils	20 (3-145)	23 (2-79)	0.004
Median units of blood	10 (0-26)	10 (3-44)	0.03
Median unit of platelets	7 (0-77)	8 (2-79)	0.006
Median days in hospital	29 (2-130)	30 (6-90)	NS
Median days of IV antibiotics	20 (2-45)	20 (0-85)	NS

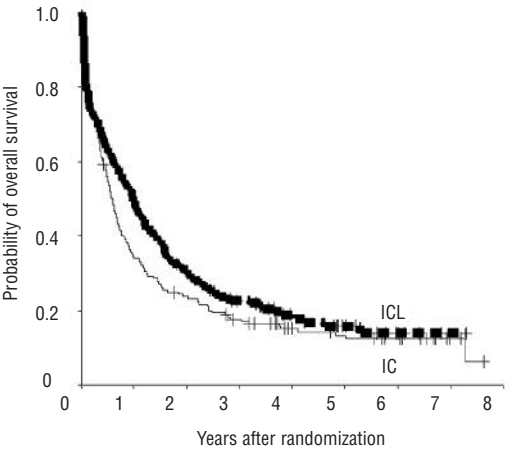
NS: non-significant; IV: intravenous.

Toxicity and supportive care by treatment arm

Most of the deaths were due to infectious disease or organ failure (Table 3). A comparison of the incidence of grade 3 and 4 toxicities between the treatment arms showed that hematologic and liver toxicities were significantly different. The median time to achieve >50×10^9/L platelets was 23 days (range, 3-119) for patients who received lomustine and 18 days (range, 0-99) for those who did not (p= 0.001). The median time to achieve >0.5×10^9/L neutrophils was 23 days (range, 2-79) for patients who received lomustine and 20 days (range, 3-145) for those who did not (p= 0.004). Time to hospital discharge did not differ significantly between the two treatment arms with estimated medians of 29 days (range, 2-130) for the IC arm and 30 days (range, 6-90) for the ICL arm. Liver toxicity was greater in patients who received lomustine but was transient (p=0.01).

Survival by induction treatment arm

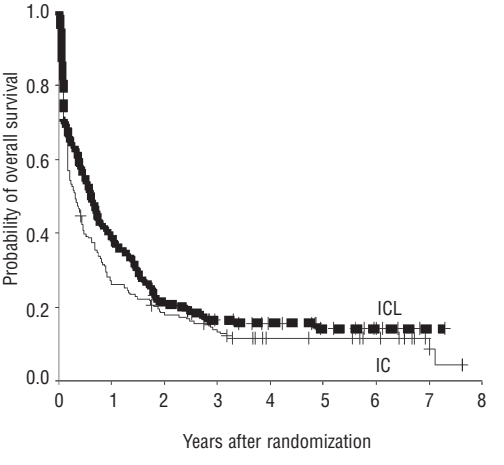
Of the 364 eligible patients, 306 died (160 treated with IC and 146 with ICL). The remaining 58 patients were reported alive between 5 and 91 months (median 49 months) after randomization. The median OS was 7 vs. 12 months in the IC and ICL arms, respectively (p=0.05). However, OS at 2 years was not statistically different, being 31±7% in ICL patients vs. 24±6% in IC patients (Figure 2). Median event-free survival (EFS) was 4 vs. 7 months p=0.06), but EFS at 2 years was not statistically different being 22% (CI 15-29%) in ICL patients vs. 18% (CI 12-24%) in IC patients (Figure 3). Of the 227 patients who achieved a CR (108 in the IC arm, 119 in the ICL arm), 144 relapsed (70 in the IC arm, 74 in the ICL arm) and 34 died without reporting any relapse (17 in each arm), with no differences between the two groups. For patients randomized to



At risk

ICL (n=178)	88	55	34	19	11	4	1
IC (n=186)	64	45	30	18	16	11	3

Figure 2. Overall survival from randomization by induction treatment. The table below the graph indicates the number of patients at risk of death at each time point (from log-rang analysis). The median overall survival (OS) was 7 vs 12 months in the IC and ICL arms, respectively (p=0.05); however, at 2 years the OS was not statistically different being 31±7% in the ICL arm vs 24±6% for patients treated with IC.



At risk

ICL (n=178)	69	36	23	17	10	6	1
IC (n=186)	48	33	23	14	0	10	3

Figure 3. Event-free survival from randomization by induction treatment. The table below the graph indicates the number of patients at risk of relapse or death at each time point (from log-rank analysis). The median event-free survival (EFS) was 4 vs 7 months in the IC and ICL arms, respectively (p=0.06); however, at 2 years the EFS was not statistically different being 22% (CI 15%-29%) for patients treated with ICL vs 18 (CI 12%-24%) for patients treated with IC.

receive IC or ICL who achieved CR, the 2-year DFS was 31% (CI 22-39%) for both groups (Figure 4). The cumulative incidence of relapse at 2 years was 55% in each group.

Post-remission therapy

Of the 227 patients who achieved CR, 27 were not registered for the first consolidation therapy (23 were unfit and four in relapse). Out of 200 patients who received the first consolidation, 101 were randomized for the second consolidation and 99 were excluded (10 were in relapse, 45 were unfit and 44 refused). The 101 randomized patients were equally distributed in the two post-remission arms. The analysis of the outcome after the second randomization between the 50 patients who received the intermediate cytarabine schedule and the 51 who did not showed no differences in 2-year OS with the rates being 47% (CI 40%-54%) and 46.5% (CI 40-54%), respectively (p=0.96).

Factors predicting outcome

Parameters that were found to be significantly associated with achievement of remission in multivariable analysis were cytogenetic group, performance status, age, and lower marrow blast percentage. Hyperleukocytosis was not a prognostic factor. Resistant disease was significantly less frequent in patients who received lomustine. OS, EFS and DFS were significantly influenced by cytogenetics and age (Table 4).

Table 4. Factors associated with achieving remission and with survival: multivariable analysis.

End point	*Favorable factors*	*Relative risk*	*95% CI*	*p*
Achieving CR	Favorable and intermediate cytogenetic	2.67	1.56-4.55	0.0003
	Performance status grade 0 or 1	2.11	1.20-3.72	0.01
	Younger patient	1.06	1.01-1.11	0.02
	Lower marrow blast percentage	1.02	1.01-1.03	0.03
	Lomustine arm	1.67	1.00-2.78	0.05
Resistant disease post-induction	Lomustine arm	0.35	0.18-0.68	0.002
	Favorable and intermediate cytogenetics	0.24	0.13-0.46	0.0001
Overall survival	Younger patient	0.66	0.52-0.84	0.0006
	Favorable and intermediate cytogenetics	0.57	0.44-0.74	0.0001
Event-free survival	Younger patient	0.96	0.94-0.99	0.001
	Favorable and intermediate cytogenetics	0.60	0.46-0.78	0.0001
Disease-free survival	Younger patient	0.71	0.52-0.96	0.02
	Lower blood blast percentage	1.01	1.00-1.01	0.03
	Favorable and intermediate cytogenetics	0.64	0.44-0.92	0.02

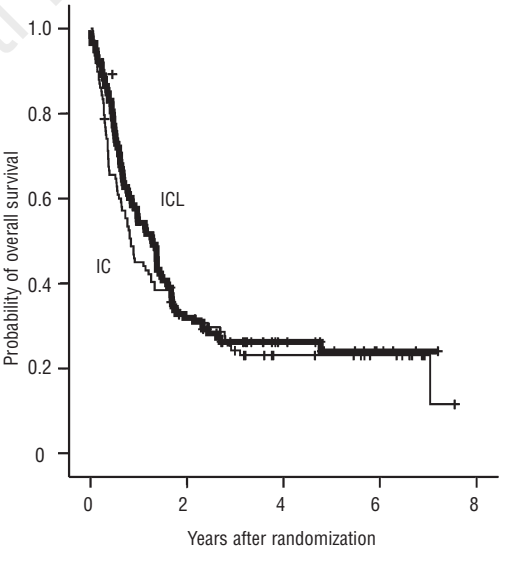


Figure 4. Disease-free survival from CR by induction treatment. The 2-year DFS was 31% (CI 22%-39%) for both groups.

Discussion

The present phase III randomized clinical trial assessed whether the use of an induction regimen with addition of lomustine to cytarabine and idarubicin was associated with improved outcome compared to that achieved with a conventional induction regimen of cytarabine and idarubicin alone. In choosing to study the ICL regimen, we expected to find an improved CR rate and survival due to greater anti-leukemic efficacy without excessive toxicity. Neither CR rates nor survival were significantly different between patients treated with ICL and IC. Despite these negative results, some encouraging points and a trend for improvements emerged that could be used for a future protocol design. The most encouraging point was the anti-leukemic efficacy of lomustine as illustrated by the reduction in chemoresistant disease, the rate of patients resistant to induction chemotherapy decreasing from 23% to 13% with the addition of lomustine (p=0.021). The second point concerns the particularly impressive CR rate (59%) in patients with poor cytogenetic features treated with lomustine compared to the rates reported in the literature. The third point concerns survival since the ICL group gained 5 months (median OS improved from 7 to 12 months with lomustine, p=0.05). Therefore a larger study with a randomization of lomustine not only for induction but also during consolidation and maintenance could demonstrate the benefit of adding this alkylating agent. The value of treating patients with alkylating agents has been recently reinforced by the promising results of a new compound – cloretazine – which in a recent trial on refractory leukemia in combination with cytarabine

gave an overall response rate of 27% in refractory patients. An international randomized phase III study is ongoing.[31]

While there was no statistical benefit from adding lomustine, there were no differences in toxic death induced by ICL compared to IC. Two toxicities were overexpressed in the ICL arm: a higher hematologic toxicity, which did not lead to longer hospitalization, and a higher but transient liver toxicity. Indeed, lomustine belongs to the family of nitrosourea drugs, which are alkylating agents known for their hematologic and liver toxicity. Other randomized studies also failed to improve the outcome of older patients by adding a third drug to the induction schedule. When tested by the CALGB group in combination with a 3+7 schedule of daunorubicin and cytarabine (DA) to form the DAT regimen,[29] thioguanine provided no benefit. In an Australian study comparing the same 3+7 DA with a combination therapy comprising etoposide plus DA, remission duration was significantly improved only in patients under 55 years of age and there was no clinical benefit for older patients.[30]

The second objective of this trial was to try to improve the results of consolidation by using an intensification schedule of intermediate-dose cytarabine (1 g/m^2×4). The objective was not achieved as the second randomization was, on the one hand, very difficult to perform and, on the other, our results showed no improvement in patients randomized to receive the intermediate-dose cytarabine. The non-feasibility of this second randomization, in which only half of the patients were randomized, was likely due to the large proportion of patients with a poor performance status at the time of randomization and to a high rate of refusal. For the randomized patients, the study failed to show any advantages as survival was identical in both groups. Our results are comparable to those of the two CALGB trials published to date. In the first report,[16] four cycles of high-dose cytarabine administered after remission and compared with less intense schedules of this drug did not provide benefits in DFS and OS in patients older than 60 years. A more recent study[5] led to the same conclusions. Therefore, intensification of cytarabine should not been recommended in the elderly.

The value of post-remission therapy is still questionable. Nevertheless, as shown by two previous EORTC/HOVON studies[6,28] in which patients were randomized between post-remission therapy and observation, only post-remission therapy was able to reduce the risk of relapse and to allow a few patients to achieve prolonged DFS. The type of post-remission therapy is also an important issue. As recently shown,[32] more prolonged treatment is preferable to intensive chemotherapy as post-remission therapy in elderly patients. In a forthcoming trial we will test a schedule of consolidation treatment with lomustine, as we think that it might prolong responses.

Authors' contributions

Conception and design of the study: A-MS, ND, FH, MA, LM, J-JS, MR, FB, GL, NG, NF, J-FR, SC and JR; analysis and interpretation of data: AP, VP, EJ, NV, NI and LRS.

Conflicts of Interest

The authors reported no potential conflicts of interest.

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