



[haematologica]
2004;89:145-153

GIMEMA ALL - Rescue 97: a salvage strategy for primary refractory or relapsed adult acute lymphoblastic leukemia

ANDREA CAMERA
LUCIANA ANNINO
FEDERICO CHIURAZZI
PAOLA FAZI
NICOLA CASCAVILLA
FRANCESCO FABBIANO
FILIPPO MARMONT
FRANCESCO DI RAIMONDO
ANNA RECCHIA
MARCO VIGNETTI
BRUNO ROTOLI
FRANCO MANDELLI
FOR THE GIMEMA GROUP

A B S T R A C T

Background and Objectives. The outcome of adult patients with acute lymphoblastic leukemia (ALL) is discouraging, only about 30% of them becoming long-term survivors. A small fraction of patients are resistant to the first line treatment, while most patients relapse within two years of achieving complete remission (CR). No standard treatment exists for refractory or relapsed patients. The GIMEMA group designed a phase II trial for adult ALL patients with refractory or relapsed disease.

Design and Methods. Patients aged >15 years with primary refractory or relapsed ALL were eligible for this study. The salvage strategy included a single high dose of idarubicin combined with high dose cytarabine, followed by consolidation therapy leading to a stem cell transplant procedure according to donor availability.

Results. From 1998 to 2002, 135 patients were enrolled. Seventy-five patients (55%) achieved CR, including 12 Philadelphia-positive cases; 44 patients had persistent leukemia and 16 died during reinduction. Fifty patients received a stem cell transplant: 19 from an HL-A identical sibling, 16 from an unrelated donor, 7 from a haploidentical relative, 2 received cord blood, and 6 had an autotransplant. The median disease-free and overall survival were both short (5.0 and 6.4 months, respectively); however, after a median follow-up of 40 months, 13 patients are alive, 10 of whom are free of disease (9 transplanted), while 3 are alive with leukemia.

Interpretation and Conclusions. The treatment induced CR in a high percentage of poor prognosis patients, thus rendering a transplant procedure feasible in most of them. However, significant rates of transplant-related mortality and post-transplant relapse encourage the search for more effective and less toxic conditioning regimens.

Key words: acute lymphoblastic leukemia, relapse, high dose chemotherapy, stem cell transplant.

From the Hematology, Federico II University, Naples (AC, FC, BR); S. Giovanni Hospital, Rome (LA); GIMEMA Data Center, Rome (PF); IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo, FG (NC); Cervello Hospital, Palermo (FF); S. G. Battista Hospital, Turin (FMar); Ferrarotto Hospital, Catania (FDR); Civil Hospital, Pescara (AR); Hematology, La Sapienza University, Rome, Italy (FMan).

Correspondence: Prof. Bruno Rotoli, Università Federico II via Pansini 5, 80131 Naples, Italy. E-mail: rotoli@unina.it

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Although complete remission (CR) rates induced by the current chemotherapy regimens for adults with acute lymphoblastic leukemia (ALL) are excellent, ranging between 70–80%,¹⁻⁴ the percentage of long-term survivors is still disappointing, ranging from 20% to 40%.⁵⁻⁷ More than 50% of patients have a relapse in their bone marrow or in extra-medullary sites. Furthermore, the proportion of patients who fail to obtain CR or have a short-lasting CR is not negligible. Age, high circulating leukemic cell count, central nervous system involvement at diagnosis, adverse cytogenetics [t(9;22), t(4;11), t(1;19)], late CR achievement and failure to respond to prednisone pre-treatment are the major factors predictive of induction failure or short remission duration.¹⁴ While the role of stem cell transplants for adult ALL patients in first CR is still a matter of debate,⁸⁻¹³ a

combined treatment strategy including a stem cell transplant is needed for patients who relapse or who fail to obtain CR after front-line induction therapy. Indeed, salvage chemotherapy, consisting of high dose cytotoxic regimens followed by stem cell transplant, has proven to be effective in a significant proportion of relapsed ALL patients.¹⁴⁻¹⁶ In this setting, two pilot studies and, more recently, a large multicenter trial conducted in children¹⁷⁻¹⁹ have shown the efficacy of the association of high-dose cytosine arabinoside (HDARAC) with a single, high dose of idarubicin. HDARAC is currently widely used to treat patients with acute leukemias, and idarubicin is an interesting drug which can be given in a single, high dose because of the long half-life of its main active metabolite, idarubicinol. This combination was introduced in 1994 by the MSKCC group for rescuing ALL patients.¹⁷ On

the basis of their experience, the GIMEMA group (Gruppo Italiano Malattie EMatologiche dell'Adulto), conducted a large multicenter trial including this combination regimen in a more complex strategy. The aims of this multicenter study were: i) to induce CR in patients with primary refractory ALL, or a further CR in relapsed patients; ii) to evaluate the acute toxicity of high-dose chemotherapy including a single, high dose of idarubicin; iii) to test the feasibility of an early stem-cell rescue, according to donor availability.

Design and Methods

Eligibility criteria

Adult patients aged 15 years or older, with refractory or relapsed ALL, even if in second relapse, were included in this study. Absence of heart, liver or kidney damage, as well as no active infection were required for inclusion in the trial. Electrocardiography and echocardiography with ejection fraction evaluation, serum transaminase and bilirubin, and serum creatinine were used to assess eligibility status. Chest X-rays were performed to exclude the presence of pulmonary infection. Written informed consent was obtained from all patients.

Treatment plan

The treatment plan included several steps. After an intensive chemotherapy course (*salvage regimen*), patients achieving CR could receive one or more *first consolidation* courses, while waiting for a transplant procedure. If no transplant was feasible, patients were given a *2nd consolidation* course and then submitted to standard maintenance therapy. An optional *third line treatment* was proposed to patients who were resistant to the salvage regimen or who relapsed before a transplant.

The salvage regimen consisted of HDARAC (3 g/m²/day i.v., in a 3 h infusion) from day 1 to day 5, plus a single, high dose of idarubicin (40 mg/m² i.v.) on day 3. Granulocyte colony-stimulating factor (G-CSF) (filgrastim and lenograstim were both allowed) was scheduled from day 7 until neutrophil recovery. No dose reduction was planned for patients over 50 years old. Since high doses of cytarabine and idarubicin penetrate the central nervous system (CNS), weekly administrations of intrathecal methotrexate (12 mg) were added only for patients with CNS leukemia and continued until the cerebro-spinal fluid was cleared of blasts. Patients aged less than 55 years who achieved CR were planned to receive a stem cell transplant procedure, according to donor availability, from an HL-A identical sibling, a matched unrelated donor, a haploidentical relative, cord blood or an auto-transplant. One or more consolidation

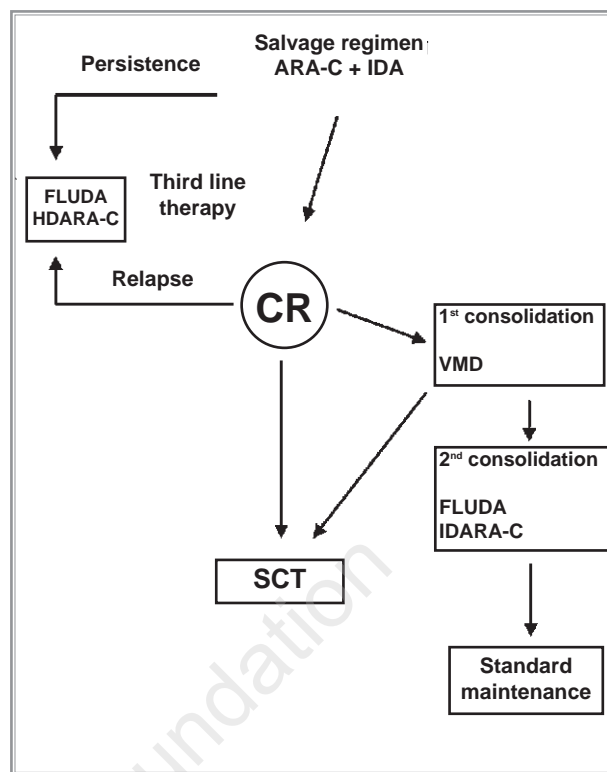


Figure 1. GIMEMA ALL-Rescue 97 treatment program. For drug doses, see text.

courses including vindesine (3 mg/m² i.v. on day 1), high-dose methotrexate (2 g/m² i.v., 6 h continuous infusion on day 1) and dexamethasone (20 mg i.v. days 1–4) (VMD), followed by leucovorin rescue, were administered to patients every two or three weeks, while waiting for the transplant procedure. Patients in CR who could not receive a transplant procedure for whatever reason were consolidated with the VMD scheme and then with an association of fludarabine (30 mg/m² i.v. days 1–3) and intermediate-dose ARA-C (500 mg/m² i.v. days 1–3) before entering a standard maintenance program which included courses of mercapto-purine (70–90 mg/m² orally) for two months associated with weekly administration of methotrexate (30 mg/m² i.m.), followed by a reinduction program with teniposide (150 mg/m² i.v.) and cytarabine (300 mg/m² i.v.) on day 1 and day 15, vincristine (1 mg/m² i.v.) and cyclophosphamide (300 mg/m² i.v.) on day 8 and day 22.

A third-line therapy with fludarabine (30 mg/m² i.v. days 1–3) and HDARAC (2 g/m² i.v. d 1–5) was also suggested for patients who failed to obtain CR after the salvage treatment and for those who relapsed after the salvage treatment before the transplant procedure (Figure 1).

Stem cell transplants were performed at the different institutions according to the Center's own transplanta-

Table 1. Response to salvage treatment.

	Refractory	Relapsed	Total
N. of patients	28	107	135
Age, median (range)	26 (16-50)	30 (15-71)	30
Complete response	16-57%	59-55%	75-55%
Leukemia persistence	9-32%	35-33%	44-33%
Deaths	3-11%	13-12%	16-12%

tion protocols, with conditioning regimens and graft-versus-host disease (GVHD) prophylaxis given according to each institution's policy.

Statistical methods

Survival distributions were estimated by the Kaplan-Meier method. Disease-free survival (DFS) was calculated from the date of complete remission achieved with the salvage regimen to the date of relapse, death in CR or last follow-up. Overall survival was defined as the time from inclusion in the study to death or last follow-up. Statistical differences in survival distributions were evaluated with the log-rank test; other correlations were evaluated by the χ^2 test.

Results

Study population

From September 1998 to September 2002, 135 patients from 25 Italian institutions from the GIMEMA Group (see *Appendix*) were enrolled. There were 74 males and 61 females, with a median age of 30 years (range, 15-71). Twenty-eight patients entered the study because of persistent leukemia after first line induction therapy, while 107 had had hematologic (95 patients) and/or extra-hematologic (12 patients) relapse, 6 of them showing CNS leukemia. Eight patients were enrolled while in second relapse.

A majority of patients had received front-line treatment consisting of a four-drug regimen followed by consolidation and standard maintenance chemotherapy, according to various GIMEMA trials: ALL-0183⁶ (n = 4), ALL-0288⁴ (n = 12), ALL-0394²⁰ (n = 10), ALL-0496²¹ (n = 76), ALL-0597²² (n = 2), and ALL-2000 (n = 6). A small group of patients had already received high-dose chemotherapy (i.e. HyperCVAD, HAM) (n = 17) or allogeneic stem cell transplant (n = 3). B-lineage ALL was documented in 67% of patients and T-lineage in 24%; a hybrid phenotype (i.e., presence of one or two myeloid markers) was observed in 9% of

patients. The Philadelphia (Ph) chromosome and/or a hybrid bcr/abl transcript were detected in 22 patients (16%), including five cases with hybrid phenotype, a figure lower than expected in a cohort of adult ALL patients; however, it should be noted that Ph⁺ ALL patients are often enrolled in specific trials. Thirteen patients showed other cytogenetic translocations: t(4;11) [n=8], t(1;19) [n=3], t(8;14) [n=2]. The median duration of the first CR in the relapsed patients was 11 months (range: 1.5 - 116).

Response evaluation

CR was achieved in 16/28 patients with refractory leukemia (57%) and in 59/107 patients with leukemia relapse (55%), for an overall CR rate of 55% (Table 1). Forty-four patients (33%) showed persistent leukemia and 16 patients (12%) died during or soon after the high-dose chemotherapy.

As for response according to leukemia phenotype, CR was observed in 52% of patients with B-lineage disease, in 56% of patients with T-lineage disease and in 70% of the few patients with hybrid ALL.

In the subgroup of 22 Ph⁺ patients, 12 cases (54%) achieved CR, whereas in the 13 patients with adverse cytogenetics other than the Ph chromosome, none reached CR (persistent leukemia in 7, early death in 6). High dose chemotherapy proved to be effective even in patients in second relapse, among whom CR was obtained in 6/8 cases (75%).

In the small group of patients enrolled after a transplant procedure, all patients achieved a second CR, but all relapsed within three months.

Looking for factors possibly related to salvage failure, we found that only adverse cytogenetics other than t(9;22) [i.e., t(4;11); t(1;19); t(8;14)] and a first CR duration \leq 24 months predicted a low CR rate. Indeed, in the group of patients who entered the trial because of relapse, response to salvage treatment in terms of CR correlated with the duration of the first CR (Figure 2).

Forty-five patients received the first consolidation therapy. Among these, five patients continued the chemotherapy program with a second consolidation course and then with maintenance chemotherapy, because they were ineligible for a transplant; all these patients relapsed and died.

Forty-one patients relapsed after achieving CR and before transplant, eleven of them within two months of having attained the CR. Statistical analysis did not reveal any factors that predicted early relapse.

Nine patients refractory to the salvage treatment received the optional 3rd line regimen (i.e., fludarabine plus HDARA-C), but none was rescued.

A flow-chart summarizing the entire study is presented in Figure 3.

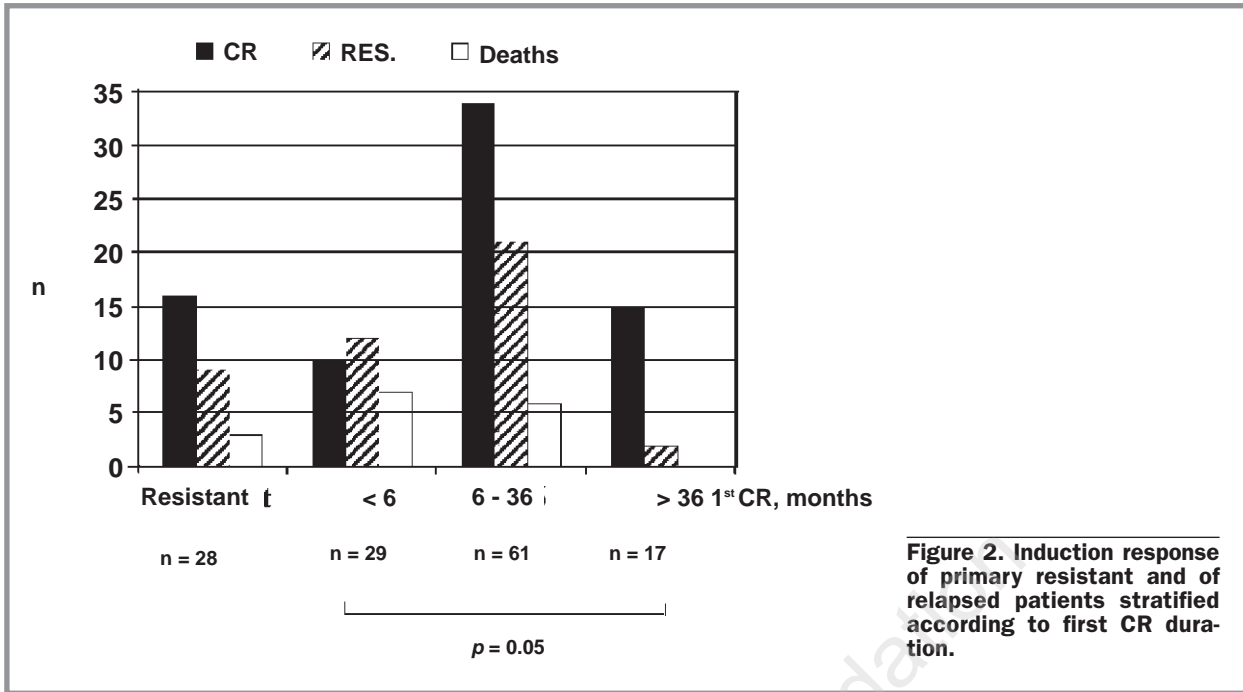


Figure 2. Induction response of primary resistant and of relapsed patients stratified according to first CR duration.

Acute toxicity

Myelosuppression was the main toxicity observed. The median time to granulocyte ($>0.5 \times 10^9/L$) and platelet ($>50 \times 10^9/L$) recovery was 27 (range, 21- 35) and 34 (range, 25-40) days, respectively. Fever ($> 38^\circ C$) for a median of 7 days (range, 2-12) occurred in 102 patients, with bacterial and/or fungal infection documented in 29. Sixteen patients (median age 28 years, range 17-56) died during the salvage chemotherapy: 3 of fatal hemorrhage (one cerebral and two gastrointestinal), and 13 of infection. Oral toxicity was observed in 27 patients, with grade III mucositis occurring in 6 patients and grade IV in one. Liver damage, documented by raised levels of serum transaminase and/or conjugated bilirubin, was reported in 19 patients. Cardiac toxicity was observed in seven patients: three showed grade III atrial or ventricular rhythm alterations, and 4 had heart failure which was fatal in two. The cases of grade 3-4 extra-hematologic toxicity are summarized in Table 2.

Table 2. Grade 3-4 extra-hematologic toxicity after the salvage high-dose therapy (WHO grading).

	Grade	n	
Heart function	3	3	} 3.7%
	4	2	
Oral	3	6	} 5.2%
	4	1	
Intestinal	3	1	0.74 %

Stem cell transplant

Fifty patients, 37% of the whole patient population, underwent a transplant from various stem cell sources. The stem cell transplant (SCT) was performed in 34 patients in CR (45% of those who had achieved CR), and in 16 patients not in CR (i.e., with a bone marrow blastosis of 6-20%, documented after salvage or in patients with initial leukemia recurrence). Nineteen patients received a transplant from an HLA-identical sibling, 16 from a matched unrelated donor, 7 from a haploidentical donor, and two received cord blood stem cells. Six patients underwent auto-transplantation: two

Table 3. Post-remission treatment.

	Refractory (n= 28)	Relapsed (n= 107)	Total (n= 135)
Patients in CR	16	59	75
Additional CHT and maintenance	1	4	5
Stem cell transplant			
HLA id. sibling	3	11	14
MUD	4	6	10
Haplo	1	5	6
Cord	1	-	1
Auto	1	2	3
Total transplanted	10	24	34

In addition, 4 patients in partial remission and 12 patients in early subsequent relapse were transplanted while not in CR (5 HLA id. Sib.; 6 MUD; 1 haplo; 1 cord; 3 auto).

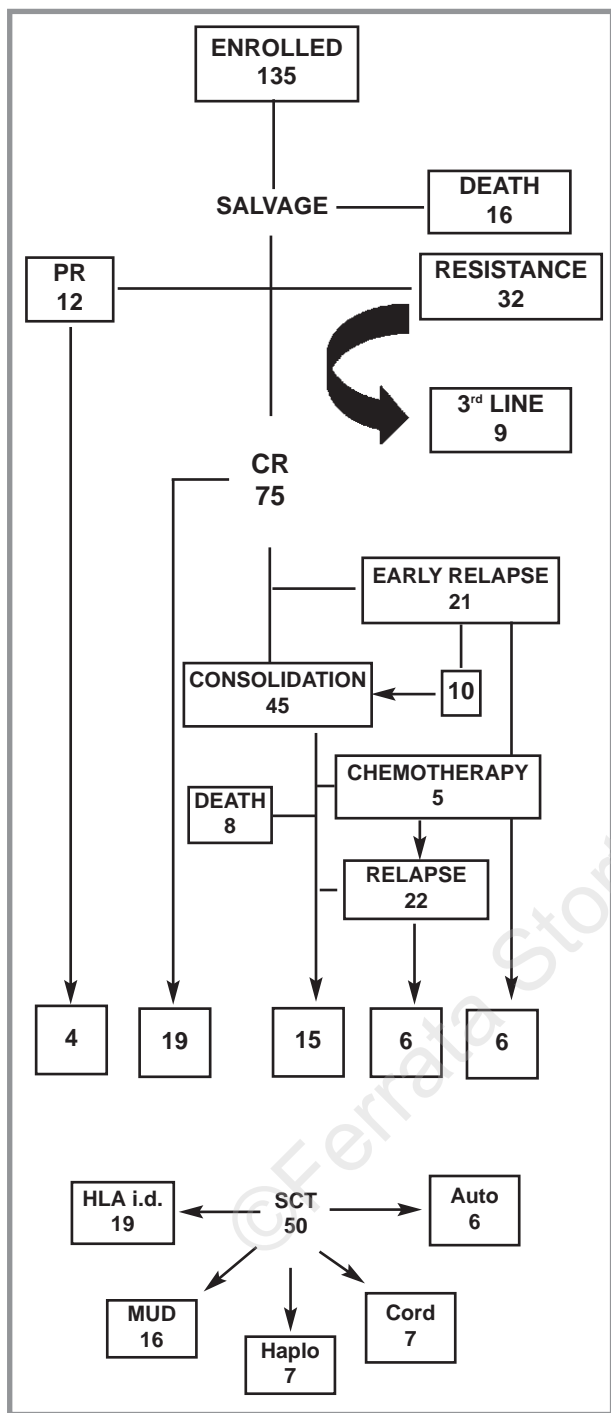


Figure 3. Flow-chart of the entire population studied.

from bone marrow and four from peripheral blood stem cells (Table 3). The median time between achieving CR and undergoing the transplant was 2.4, 4.7, and 6.3 months for patients transplanted from an HL-A identical sibling, from a haplo-identical relative and from a matched unrelated donor, respectively, and four months

for those who received cord blood cells. The conditioning regimens given are summarized in Table 4. Transplant-related mortality (TRM) was 16 % (3/19) for patients who received an HL-A identical sibling transplant, 31% (5/16) for those transplanted from a matched unrelated donor (MUD) and 57 % (4/7) for those who received stem cells from a haploidentical donor; finally, one of the two patients who received cord blood cells succumbed to transplant-related mortality (TRM). After a median follow-up of 42 months (range, 6-60), 8 patients transplanted in CR are alive and disease free, while 18 relapsed in a median time of six months (range, 2-32) after transplantation (Table 5). Among the group of patients who were transplanted while they were not in CR (n= 16) only one (MUD) is alive and disease free; five patients (transplants from HLA-identical sibling, 3; MUD, 1; haploidentical donor, 1) succumbed to TRM, two patients (1 HLA-identical sibling; 1 MUD) relapsed early and eight (4 HLA-identical sibling; 1 MUD; 1 haploidentical donor; 2 auto-transplant) showed persistent leukemia at hematologic reconstitution.

Survival analysis

Median overall (OS) and disease-free (DFS) survival were 6.4 (range, 0.2-58.6) and 5.0 months (range, 0.7-57), respectively (Figures 4 and 5). Survival curves did not differ when the patients were stratified by age groups (i.e., <30, 30-50, >50). The estimated overall survival was the same in the series of patients with primary resistant disease and those who had relapsed. After three years, 10% (CI 95%: 4.1-15.9) of the whole patient population is projected to be alive and 16% (CI 95%: 7.8-23.4) of the patients who achieved CR are projected to be disease-free. A comparison of the OS curve of the entire population in study including the post-transplant period and the same survival curve in which transplanted patients were censored at the time of their transplant (Figure 6) seems to suggest that SCT improves survival; however, the difference is not statistically significant.

The overall survival of those patients who entered the study because of leukemia relapse correlated with the duration of the first CR. Indeed, the median survival was 5.3 months for patients whose first CR lasted ≤ 24 months (n= 79), and 11.5 months for patients whose first CR lasted longer than 24 months (n=28) ($p = 0.001$) (Figure 7). Of the 12 patients with Ph⁺ ALL who achieved CR, six relapsed early, in a median time of 2.5 months (range, 1-6), while six patients underwent a SCT (3 HLA-identical sibling; 2 haploidentical donor; 1 autotransplant). Of the Ph⁺ transplanted patients, two succumbed to TRM, one showed disease progression and three patients relapsed.

On the whole, at a median follow-up of 40 months

Table 4. Conditioning regimens according to the type of transplant.

Regimen	Sibling	MUD	Haplo	Cord	Auto	Total
BU CY2*	11	9	1	–	4	25
CYTBI°	7	1	–	2	–	10
Thio CY	–	6	–	–	–	6
Fluda Thio ATG	–	–	6	–	–	6
DXM CY	1	–	–	–	–	1
HDVP16	–	–	–	–	1	1
Ara-C MPH	–	–	–	–	1	1
	19	16	7	2	6	50

*Including +Idarubicin (2 cases), + ATG (1 case), + VP16 and ATG (1 case); °including + ATG (1 case), + Thio (1 case) ATG: anti-thymocyte globulin; DXM: Daunoxome; Thio: Thiotepa; MPH: Melphalan.

Table 5. Outcome of transplanted patients.

	HLA id. sibling	MUD	Haplo	Cord	Auto
No. of patients	19	16	7	2	6
TRM	3	5	4	1	–
Leukemi persistence or relapse	11	7	3	1	6
Patients in CCR	5	4	–	–	–
Overall survival*	15	15	10	–	6
CCR duration*	10	9	6	–	3

*Months, median, from the date of entering the study.

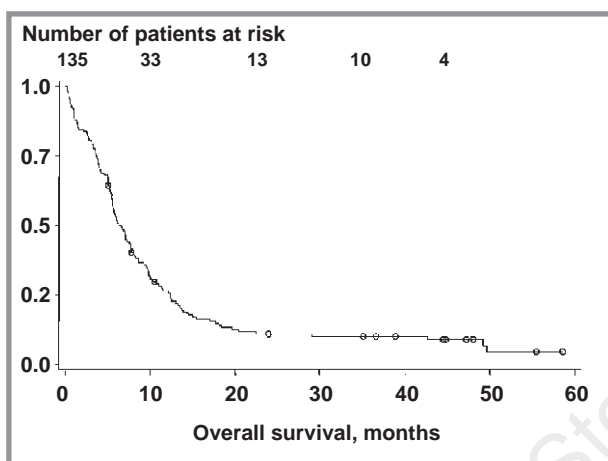


Figure 4. Estimated overall survival by the Kaplan-Meier method in the whole cohort of patients.

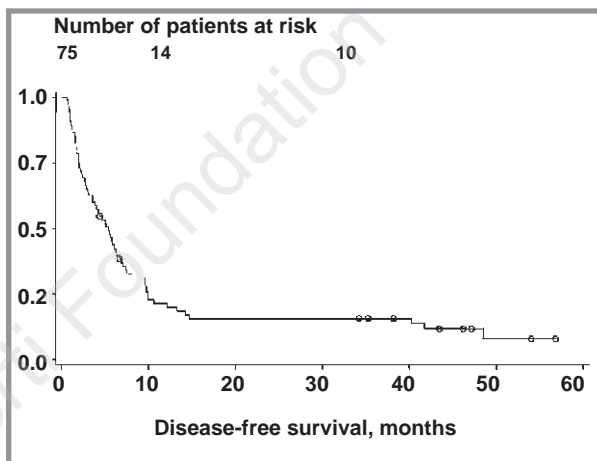


Figure 5. Estimated disease-free survival by the Kaplan-Meier method (only patients who achieved CR).

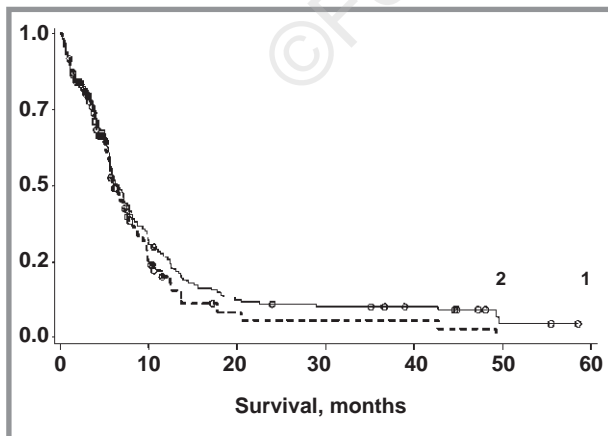


Figure 6. Effect of the transplantation procedures on the OS of the entire series (n= 135). Plot # 1: all patients including the post-transplant period; Plot # 2: all patients, with transplanted patients censored at the date of transplant.

(range, 5–59), 9 transplanted patients are alive and disease-free, 3 patients are alive with leukemia (two of them after a transplant), and one non-transplanted patient is in continuing CR after a short follow-up (8 months).

Discussion

Because of the large proportion of adult ALL patients who relapse, a salvage strategy is required to rescue these patients after first line treatment has failed. We carried out a multicenter trial on salvage treatment of adult patients with primary refractory or relapsed ALL, incorporating the MSKCC regimen in a more complex strategy including a transplant procedure, when feasible.

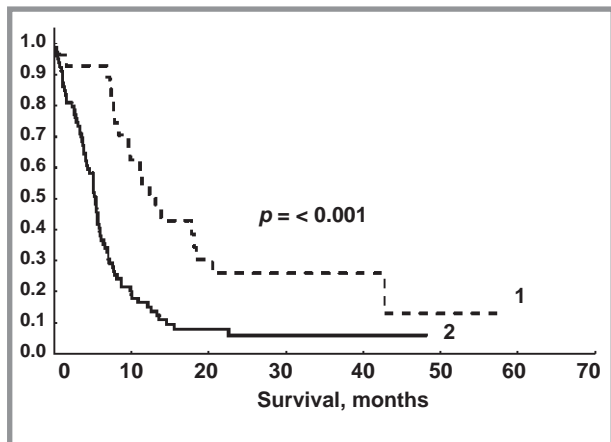


Figure 7. Estimated overall survival for relapsed patients according to duration of the first CR. Plot #1: >24 months (n=28); plot #2: ≤ 24 months (n= 79).

The observed CR rate (55%) can be considered excellent in this group of poor prognosis patients, which included patients with primary refractory disease and those carrying the Ph chromosome. The combination of two highly active drugs in an intensified scheme has potent antileukemic activity, even in the presence of various types of drug resistance. As already observed in Ph⁺ ALL patients after first line treatment, the remission rate was high even in relapsed patients, but the cure rate was poor because of early relapse. In the present study, no patient received imatinib because they were enrolled in the pre-Gleevec era; however, the relatively high CR rate achieved in this protocol could be a basis for subsequent imatinib treatment in future patients. On the other hand, our salvage treatment proved to be ineffective in patients with other types of adverse cytogenetics [t(4;11); t(1;19); t(8;14)]. The rate of deaths during induction (12%), mainly due to severe infection, was acceptable in this setting of heavily treated patients. On the whole, there were no statistically significant differences between resistant and relapsed patients. As reported in other studies,²³ the outcome in the group of relapsed patients was related to the duration of the first CR: the longer the first CR, the better the outcome, in terms of both CR rate and survival. Although the numbers in subgroups are small, our data show that the poorest results in terms of CR rate were obtained in patients relapsing within 6 months of diagnosis. Indeed, 10/29 (34%) patients whose first CR lasted <6 months reached CR after the salvage treatment, compared to 34/61 (56%) for those relapsing while in maintenance treatment and to 15/17 (88%) for those relapsing while off treatment (> 36 months) (Figure 2). The results for patients

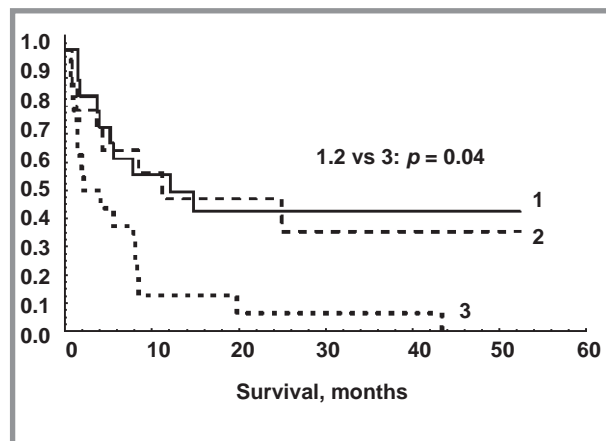


Figure 8. Estimated survival of transplanted patients, calculated from the date of transplant, according to the type of transplant: plot #1: SCT from HL-A identical sibling (n=19); plot #2: SCT from MUD (n= 15); plot #3: SCT from haploidentical donor (n= 7), from cord blood (n= 2) and autotransplant (n= 6), all together.

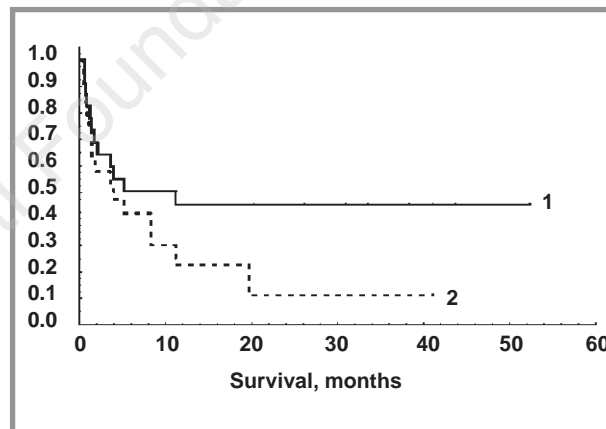


Figure 9. Estimated survival from the date of transplant for patients transplanted in CR (n= 34) (plot # 1) or not in CR (n = 16) (plot # 2).

relapsing within 6 months of diagnosis were even worse than those obtained in patients resistant to the first line treatment, who showed a CR rate of 56 %. There are two, not mutually exclusive explanations for this finding: (i) patients entered for refractory disease had received only a month or two of chemotherapy, while patients relapsing within 6 months had received prolonged cytotoxic treatment (induction, consolidation); (ii) the early relapse group included more patients with adverse cytogenetics, who had a short-lasting first CR.

Acute toxicity was negligible: only a small number of patients experienced grade III-IV organ damage. Despite the scheduled high-dose anthracycline, severe heart dysfunction was observed in only four cases, two

of which were fatal. It should also be noted that no severe gut toxicity (i.e., gut-syndrome, ileotyphlitis) was observed. The third line chemotherapy designed to rescue patients not responding to the salvage regimen (fludarabine combined with HDARA-C) was ineffective in inducing any further CR. This observation is in agreement with the analysis performed by Thomas *et al.*²⁴ on various trials conducted in patients with relapsed acute myeloid leukemia, in whom fludarabine-containing regimens did not show beneficial effects when compared with similar schedules not including fludarabine.

Stem-cell transplant could be performed in a relatively large number of patients who were eligible for this procedure. It is noteworthy that 9 of the 10 patients who are alive in continuous CR had received stem cell rescue. A better survival was noted for patients transplanted from a HLA-identical sibling or from a matched unrelated donor; the survival results in these two sets of patients were similar (Figure 8), since an increased transplant-related mortality in the MUD group was balanced by a lower relapse rate (Table 5). A similar finding was recently reported for a series of 623 transplanted adult ALL patients collected by the European Bone Marrow Transplantation Registry.²⁵ The use of matched unrelated donors is going to increase in several countries, thanks to more precise molecular matching and faster identification of a donor worldwide. If the lower relapse rate in MUD transplanted patients is due to a stronger graft-versus-leukemia effect, then the possibility of reducing TRM by using less intensive conditioning regimens could be explored in this setting.

As could be expected, the outcome of patients who were transplanted while not in CR was poor (Figure 9). In comparison to findings in a previous study from the GIMEMA group on the same topic,²³ we observed a sim-

ilar CR rate in a wider cohort of patients (135 vs 61), which included categories of patient who were excluded from the previous study (those resistant to first line treatment, those in second relapse, and 3 patients over 55 years old). In addition, in the previous study only 5 patients received an allogeneic transplant, and none was grafted from a MUD, while in this study 44 patients received an allogeneic transplant, 16 from a MUD. The present OS curve of patients transplanted in CR shows an interesting 46% alive at 3 years (Figure 9), which compares favorably with the curve of non-transplanted patients in this and in the previous study. In conclusion, this multicenter trial shows the efficacy of a combined high-dose regimen in inducing CR in relapsed or refractory adult ALL patients, with excellent tolerance even in heavily pretreated patients, and proves the feasibility of transplant procedures. However, the rate of post-transplant relapse remains unacceptably high, highlighting the need for different conditioning regimens aimed at reducing TRM and increasing a possible graft-versus-leukemia effect.

AC, LA, and BR were the main investigators who critically analyzed the data. AC collected patients' data and wrote the paper; FC, NC, FF, FM, FDR, and AR had full responsibility for the patients' care and management; PF and MV performed statistical analysis; LA, BR and FM designed the study, revised the manuscript and gave the final approval for its submission. All the authors gave their contribution to the manuscript. Primary responsibility for the paper, figures and tables: AC, LA, BR and FM. The authors acknowledge the active cooperation of all colleagues listed in the Appendix and are grateful to Sandra De Simone, Francesca Paoloni and Ciro R. Rinaldi for data collection and help in analysis. Helpful discussions with Prof. G. Meloni and Prof. W. Arcese are fully acknowledged. The authors indicate no potential conflicts of interest.

Received on October 27, 2003, accepted December 1, 2003.

Appendix

Participating Centers and number (#) of patients enrolled.

Università Federico II, Napoli (Prof. Bruno Rotoli) #20; IRCCS Casa Sollievo della Sofferenza, S. Giovanni Rotondo (Prof. A. Michele Carella) #16; Università La Sapienza, Roma (Prof. Franco Mandelli) #13; Ospedale Cervello, Palermo (Dr. Salvatore Mirto) #10; Ospedale S. G. Battista, Torino (Dr. Eugenio Gallo) #9; Policlinico, Catania (Dr. Rosario Giustolisi) #8; Ospedale Civile, Pescara (Dr. Giuseppe Fiorioni) #7; Università di Modena (Prof. Giuseppe Torelli) #6; Ospedale Civile, Avellino (Dr. Ettore Volpe, Dr. Nicola Cantore) #6; Università, Bari (Prof. Vincenzo Liso, Prof. Giorgina Specchia) #5; Università, Bologna (Prof. Michele Baccarani, Dr. Pierpaolo Piccaluga) #5;

Ospedale S. Martino, Genova (Dr. Gino Santini, Dr. Raffaella Cerri) #5; Università di Pisa (Prof. Mario Petrini) #4; Ospedale Civile, Reggio Calabria (Dr. Francesco Nobile) #4; Ospedale Civile, Catanzaro (Dr. Antonio Peta) #3; Università Cattolica, Roma (Prof. Giuseppe Leone) #3; Università, Ferrara (Prof. Gian Luigi Castoldi) #2; Ospedale S. Giovanni Bosco, Napoli (Dr. Eustachio Miraglia) #2; Ospedale Civile, Alessandria (Dr. Alessandro Levis) #1; Università di Ancona (Prof. Pietro Leoni) #1; Università, Palermo (Prof. Guglielmo Mariani) #1; Università di Parma (Prof. Vittorio Rizzoli) #1; Ospedale S. Giovanni, Roma (Dr. Luciana Annino) #1; Ospedale Civile, Taranto (Dr. Patrizio Mazza) #1; Ospedale Maggiore Carità, Novara (Dr. Giancarlo Avanzi) #1.

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