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Intensive salvage chemotherapy for primary refractory or first relapsed adult acute lymphoblastic leukemia: results of a prospective trial

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ABSTRACT

Background and Objective. **Adults with primary refractory or relapsed acute lymphoblastic leukemia (ALL) have a very poor prognosis with current salvage chemotherapies. Complete remissions (CR) can be obtained with intensive regimens in 40-60% of cases, but they are short-lived. In an effort to obtain high CR rates and prolong their duration and achieve long-term survival in a substantial number of patients, we designed an intensive combination salvage regimen (RELAL-88). In this protocol, chemotherapy was to be followed by an allogeneic or autologous stem cell transplant (SCT) within three months from CR.**

Design and Methods. **Forty-five patients with primary refractory (n=17) or first relapsed ALL (n=28) were treated with the RELAL-88 five-day induction regimen comprising vindesine, mitoxantrone, cyclophosphamide, intermediate-dose Ara-C, prednisolone and methotrexate. Twenty-eight patients received granulocyte colony-stimulating factor (G-CSF), 16 patients from day 6 (early G-CSF group) and 12 from day 14 of therapy (delayed G-CSF group).**

Results. **Thirty-four patients (74%) achieved CR (95% CI 60-87), two died in aplasia due to infection and nine were non-responders. No pretreatment variable analyzed was predictive of the chance of obtaining CR. Recovery of neutrophils occurred at a median of 29 days from the start of chemotherapy without G-CSF and 20 days with G-CSF (p = 0.005), without differences between the early and late G-CSF groups. Non-hematologic side effects were usually well tolerated and consisted mainly of infections and mucositis. Twenty-three of 34 patients (68%) who achieved CR reached the planned SCT (nine autologous and 14 allogeneic). The median overall survival was 5.7 months, and the median disease-free survival for those achieving CR was 4.6 months. Among the variables analyzed for their influence on overall survival among the 34 patients who achieved CR, only the availability of an HLA-compatible sibling was associated with a prolonged survival (p = 0.03).**

Interpretation and Conclusions. **The RELAL-88 intensive salvage regimen produces a very high rate of CR in poor-risk adult ALL. Non-hematologic toxicities were tolerable, and most eligible patients could undergo the planned SCT. G-CSF significantly shortened the period of neutropenia by about eight days, irrespective of whether it was started early or late after chemotherapy. However, as with other currently available salvage therapies, remissions were short-lived, and more effective post-remission treatment strategies are needed. In our experience, only allogeneic SCT offered the chance of long-term survival.**

Key words:

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Adult patients with ALL refractory to primary induction chemotherapy (CT) or who relapse following a first remission have a very poor short-term prognosis.[1] Although complete remissions (CR) can be obtained in 40 to 70% of cases with salvage CT, these usually last less than five months, regardless of the postremission therapy applied, and with CT alone less than 5% are alive two years from the start of salvage CT.[1,2] For this reason, most physicians attempt to increase the disease-free survival by performing a peripheral blood or bone marrow transplantation (BMT, allogeneic or autologous), although the real benefit of such a strategy remains uncertain.[1,3] We designed an intensive salvage CT program with the intention of obtaining high CR rates which would allow the maximum number of patients to proceed to a stem cell transplantation (SCT).

Design and Methods

Between 1988 and December 1997, 45 consecutive eligible adults with ALL refractory to first-line conventional CT or in first relapse were enrolled in this trial. Immunophenotyping studies were performed in all cases and cytogenetic studies in 31/45 cases, either at diagnosis or at entry into the study. Other inclusion criteria were age ≥ 16 and ≤ 65 years

Table 1. Patients' characteristics.

Total no. of patients	45
Age (median,range)	30 (16-62)
Sex (M/F)	29/16
Immunophenotype	
T-ALL	7
precursor B-ALL	30
My+ B-ALL	8
Cytogenetics	
not done	14
clonal abnormalities	16*
no mitosis	6
normal	9
Status at salvage	
first relapse	28 (median 14 mo., range 2-104)
early relapse (<12 mo.)	13 (median 5.4 mo., range 2-10.5)
late relapse(> 12 mo.)	15 (median 23.5 mo., range 13-104)°
primary refractory#	17

*My+ B-ALL, myeloid antigen positive B-lineage ALL; mo. = months. *Seven patients were Ph'-chromosome positive; °3 cases were in relapse 12, 26 and 34 months after an ABMT; #started salvage chemotherapy a median of 35 days (range 22-46) from starting first-line chemotherapy.*

and lack of concomitant respiratory, cardiac, renal or liver disease which could limit tolerability to intensive CT.

The patients' characteristics are summarized in Table 1. There were 29 men and 16 women with a median age of 30 years (range 16-62). Thirty patients had precursor B-ALL, seven had T-ALL and eight had myeloid-antigen positive B-lineage ALL. Cytogenetic studies were not done in 14 cases, while 16 cases had an abnormal karyotype (including seven with the Ph'-chromosome), nine had a normal karyotype and no mitoses were obtained in six. Seventeen patients were refractory to conventional first-line CT, starting salvage CT at a median of 35 days (range 22-46) from the initiation of front-line CT. Twenty-eight patients were in first relapse; the median duration of the first CR was 28 months (range 2 to 105), being less than 12 months in 13 cases and greater than 12 months in the other 15. The latter group included three patients who relapsed 14, 26 and 34 months after an autologous bone marrow transplantation (ABMT). First-line CT for most patients consisted in the Spanish collaborative protocols PETHEMA-89 and PETHEMA-93.[4]

RELAL-88 protocol

The salvage CT regimen[5] consisted in vindesine, 2 mg/m^2 intravenously (iv.), on day 1; mitoxantrone, 12 mg/m^2 iv., on days 1, 2 and 3; cyclophosphamide, 1.5 g/m^2 iv., on day 1; intermediate-dose Ara-C, 1.2 g/m^2 as a 2-hour iv. infusion every 12 hours, on days 1, 2, 3 and 4; prednisolone, 80 mg/m^2 iv. on days 1, 2, 3 and 4; and methotrexate, 500 mg/m^2 iv. (1/3 of dose as iv. push, 2/3 as a 4-hour infusion), on day 5. Dexamethasone eyedrops were given every 8 hours until 24 hours after the last dose of Ara-C. The first 17 patients did not receive any growth factors, but the following 28 received granulocyte colony-stimulating factor (G-CSF, 5 µg/kg/day sc), 16 patients from day 6 (early G-CSF group) and 12 from day 14, until neutrophil recovery (delayed G-CSF group). Patients achieving CR were to proceed directly to allogeneic or autologous SCT within three months. If this procedure could not be performed shortly after CR, consolidation CT was administered consisting in a second course of the same regimen (n=5) or one cycle of ifosfamide, 5 g/m^2 iv. on day 1; Ara-C, 1.2 g/m^2 as a 2-hour iv. infusion every 12 hours, on days 1-4; and etoposide, 100 mg/m^2 on days 1-4 and methylprednisolone, 80 mg/m^2 on days 1-5 (n=5). Treatment-related toxicity was graded according to the WHO criteria,[6] and definitions of CR, non-response and early death followed standard criteria.[2,5]

Statistical methods. The closing date for analysis was August 31, 1998. Overall survival (OS) was calculated from the start of salvage CT until death from any cause or last control for survivors, while remission duration and disease-free survival (DFS) were calculated from CR until relapse, death from any cause or last control for survivors. The chi-square statistic was used to establish differences in the distribution of discontinuous variables and Student's t test or Mann-Whitney's U test to compare continuous variables. Kaplan-Meier product-limit estimates were used to prepare curves of DFS and OS, and differences between curves were calculated using the log-rank test. Multivariate analysis of variables predictive of obtaining CR was done by logistic regression, while multivariate analyses of DFS and OS were done with Cox's regression. Tests of significance were two-sided, with a significance level of $P \leq 0.05$.

Results

Table 2 summarizes the results of salvage therapy. Thirty-four patients achieved CR following salvage CT (76%, 95% CI 60%-87%), whereas nine patients (20%) were refractory and 2 died during the aplastic period, one from a bacterial infection and one from a fungal infection. The CR rate was similar in primary refractory (15/17, 88%) and relapsed patients (19/28, 68%) [p=0.3], without differences between early and late relapses (69% and 67%, respectively). Among those who achieved CR, the median duration of remission was only 4.6 months (range 1-108), without differences between refractory or relapsed cases (data not shown).

Forty (89%) and 39 (87%) patients recovered > 0.5×10^9/L neutrophils and > 50×10^9/L platelets, respectively. Neutrophil recovery occurred at a median of 24 days (range 11-43) from the start of CT. The median recovery time for neutrophils in 15 evaluable patients who did not receive G-CSF was 29 days (range 21-43, 95% CI 26-33) and in 25 evaluable cases who received G-CSF post-CT was 20 days (range 11-39, 95% CI 18-24); this difference is statistically

Table 2. Results of salvage chemotherapy.

Overall CR (%, 95% CI)	34/45 (76%, 60-87)
No response	9 (20%)
Early death	2 (4%)
CR according to disease status	
primary refractory	15 (88%) p =0.3
early relapse	9 (69%)
late relapse	10 (67%)*
Duration of CR (mean,range)	5.4 mo.(1-108)
Post-remission therapy°	
Did not proceed to SCT	11/34 (32%)
relapse before SCT	10@
fungal infection	1
Proceeded to SCT	23/34 (68%)
autologous SCT	9
allogeneic SCT	14
Outcome following SCT	
autologous SCT	
TRM	1
relapse	8
AWD	0
allogeneic SCT	
TRM	4
relapse	2
AWD	8#

*CR, complete remission; mo., months; SCT, hematopoietic stem cell transplantation; TRM, transplant-related mortality; AWD, alive without disease after transplant. *2/3 patients in relapse after an ABMT achieved CR. °post-remission therapy of the 34 patients who achieved CR. @duration of CR a median of 2.5 months (range 1-4). Eight patients relapsed before a planned autologous SCT and 2 during an unrelated donor search. #median 47 mo., range 4-102 after transplant.*

significant (p=0.005), being similar in the early and delayed G-CSF groups. Specifically, 13 evaluable patients in the early G-CSF group and 12 in the delayed group recovered their neutrophil count at a median of 19 (range 11-29) and 21 days (range 17-39), respectively (p=0.1). Platelet recovery occurred at a median of 24 days (range 13-90), with no differences between groups.

Extrahematologic toxicities of the salvage CT are detailed in Table 3. There were two treatment-related deaths during pancytopenia one from a bacterial and one from fungal infection. The major toxicities involved the gastrointestinal tract, with grades 3/4 nausea/vomiting, mucositis, diarrhea or hepatic abnormalities affecting 9-27% of cases. Other toxicities were uncommon and never severe. All but one patient developed neutropenic fever, with bacteremia in eight cases, pneumonia in six (one fatal pneumonia due to *Klebsiella pneumoniae*) and four probable or definite invasive fungal infections (one fatal pulmonary aspergillosis and one disseminated mucormycosis which precluded ABMT).

TABLE 3. Extrahematologic toxicity of salvage chemotherapy.

Toxicity	*N° (%)*	*WHO grades 1-2*	*WHO grades 3-4*
Conjuctivitis	3(7%)	3	–
Mucositis	29 (64%)	17	12
Nausea/vomiting	29 (54%)	24	5
Diarrhea	22 (49%)	19	3
Hepatic	14 (31%)	13	1
Renal	3 (7%)	3	–
Skin	5 (11%)	3	1

Post-remission outcome

Post-remission therapy is detailed in Table 2. Of the 34 patients who achieved CR, 11 (32%) did not reach SCT due to early relapse (n=10) occurring at a median of 2.5 months (range 1.5-3.5) from CR or fungal infection (n=1). Twenty-three patients (68%) proceeded to SCT. Nine patients received an autologous SCT (autoSCT, ABMT in eight, peripheral blood stem cell transplantation in one), which included purging by immunologic methods in eight instances,[7] and 14 patients received an allogeneic SCT (alloSCT, BMT in seven, peripheral blood stem cell transplant in seven). The median time interval from CR to SCT was 2.5 months (range 1-8) for both types of transplants. At transplant, all autoSCT recipients were in CR while 5/14 alloSCT recipients were in early marrow relapse. Of note, all 14 patients with a donor and age < 55 years underwent an alloSCT, while of the 20 patients without a sibling donor only nine reached the planned autoSCT (Table 2).

One of the nine autoSCT and 4/14 alloSCT recipients died from transplant-related complications. The remaining eight autoSCT relapsed a median of seven months (2-30) after transplant; one is alive 41 months after radiotherapy for a localized skin relapse and one is undergoing an unrelated donor BMT 14 months after relapse in third CR. Two alloSCT recipients relapsed, and 8/14 are alive and disease-free at a median of 47 months (range 4-102).

The median OS for the 45 patients is 5.7 months (range 0.2-108.95% CI 2.6-8.8), with an estimated 2-year OS of 25% (Figure 1). For the 34 responders, the median DFS is 4.6 months (range 1-109, 95% CI 1.9-7.3), with a 2-year estimated DFS of 25%. For the 23 patients who received a SCT, the median OS for autoSCT recipients is 15.4 months (range 3-41, 95% CI 8-25.8) and for alloSCT recipients the median OS has not been reached (Figure 2). By log-rank analysis, this difference is not statistically significant (p=0.2).

Prognostic factors

The probability of obtaining CR was not influenced by patient's age (< 35 vs ≥ 35 years), sex, karyotype, immunophenotype, disease status at salvage CT, tim-

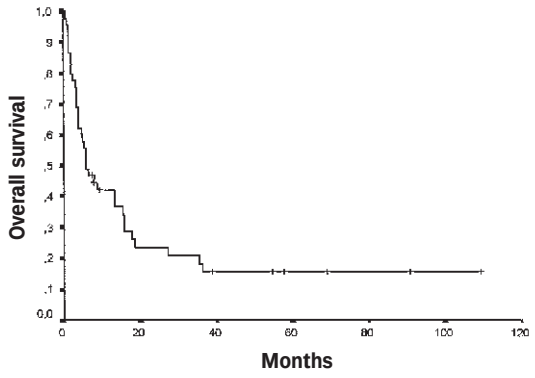

Figure 1. Overall survival from start of RELAL-88 salvage chemotherapy in all 45 patients.

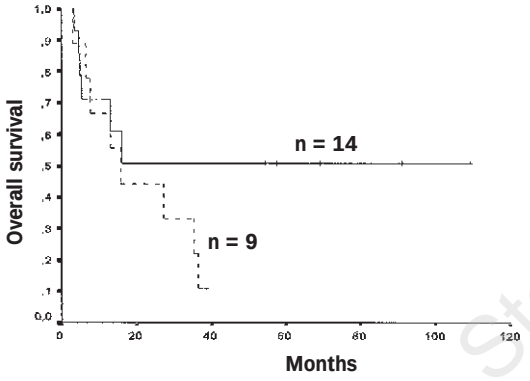

Figure 2. Overall survival from complete remission in 23 patients who received an allogeneic (——) or autologous (- - -) transplant (log-rank, p = 0.2).

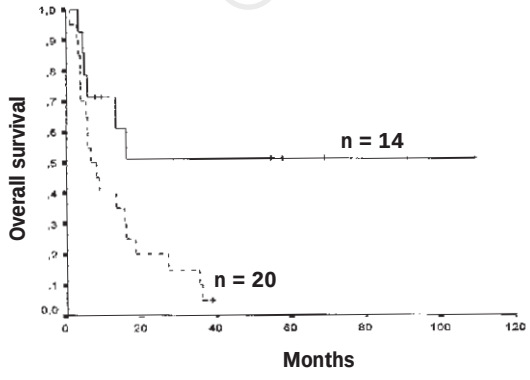

Figure 3. Overall survival from complete remission in 34 patients according to the availability (——) or not (·····) of an HLA-identical sibling donor (log-rank, P=0.016).

Table 4. Factors influencing overall survival following CR.

	#	*Median OS (95% CI)*	*Univariate p value*
Age			
< 35	17	4.3 (4.2-22)	0.8
≥ 35	17	4.8 (2.6-7.2)	
Sex			
male	23	5.6 (3.8-7.4)	0.7
female	11	5.7 (0.1-14.4)	
Karyotype			
normal	6	16 (15.8-16.2)	0.08
Ph+/other clonal abnormalities	13	5.7 (4-7.39)	
Disease status			
primary refractory	15	4.3 (4.6-21.5)	0.4
relapse	19	4.7 (2.5-6.9)	
Timing of relapse			
early	9	3.5 (1.5-5.6)	0.08
late	10	5.4 (1.4-9.4)	
Donor availability			
yes (and age ≤ 55 yr.)	14	NR	<0.01*
no	20	2.4 (1.8-11.1)	
Post-remission SCT			
no	11	3 (1-4)	0.2
autologous SCT	9	4 (8-24)	
allogeneic SCT	14	NR	
Treatment date			
before 1994	17	4.7 (2-7.3)	0.8
during/after 1994	17	7.8 (3.9-11.8)	

*NR, not reached; SCT, hematopoietic stem cell transplantation; yr., years. *in a multivariate analysis by stepwise logistic regression including age, sex, karyotype, disease status, treatment date, donor availability and post-remission treatment, the only variable associated with a prolonged OS following CR was having an HLA-identical sibling donor (p = 0.03).*

ing of relapse or treatment date (before versus during/after 1994) either in univariate nor in multivariate analyses (data not shown).

Table 4 shows the median OS in the 34 patients who achieved CR according to eight variables. By univariate analysis only having an HLA-identical sibling donor was associated with prolonged survival (p<0.01). This was confirmed in a multivariate analysis including age, sex, karyotype, disease status, treatment date, donor availability and post-remission treatment, where the only variable associated with a prolonged OS following CR was having an HLA-identical sibling donor (P = 0.03). Figure 3 shows the Kaplan-Meier OS curves corresponding to these two patient groups, which are significantly different by a log-rank test (p = 0.016).

Discussion

Currently available salvage regimens for adults with relapsed or refractory ALL produce CR in 20-70% of cases, but these remissions last less than five months in most cases. At 12 months the DFS is usually 5% or less, and no consolidation or maintenance CT offers lasting remissions.[1,2,8,9] Our 78% CR rate compares

favorably with the best results reported in the literature;[1,2,9] Giona *et al*.[8] reported a 56% CR rate, and a German study showed a 64% CR rate.[10] Both of these studies, however, were multicenter, and the patient characteristics may not be comparable to our series. By univariate analysis, we did not find that characteristics such as age, sex, cytogenetic group or duration of previous CR predicted achievement of CR. This contrasts with other studies that found that duration of previous CR,[10] and other pretreatment variables[1,8] were of predictive value. The small number of patients in each subcategory may also preclude the identification of significant differences which could otherwise become apparent with larger patient populations.

Our salvage regimen was relatively well tolerated, with only two treatment-related deaths. As expected, prolonged pancytopenia and life-threatening infections were the main toxicities observed. The use of G-CSF shortened the period of neutropenia by about eight days, as seen in other intensive chemotherapy regimens for ALL and acute myelogenous leukemia.[11] There were no differences between the early and delayed start of G-CSF after chemotherapy, with median values of around 20 days. This same finding has been reported following autologous BMT,[12] although its final clinical implications remain controversial.[13]

Since remissions are of short duration in this setting, our protocol was designed to perform an autologous or allogeneic SCT to all patients as soon as possible after CR in the hope that this would lead to lasting remissions in a higher proportion of cases. However, 32% of those who achieved CR did not undergo the procedure, usually due to early relapse. Additionally, none of the nine patients who received an autoSCT remains in remission. Thus, it appears that autologous transplantation, even with purged stem cells, offers little benefit to these patients. Allogeneic SCT using histocompatible family donors, on the other hand, offers a potential for cure in 10-40% such patients,[1] which is confirmed by our 50% long-term DFS. The prominent prognostic relevance in terms of survival of having an HLA-identical sibling was confirmed in univariate and multivariate analyses in our series of 34 patients who achieved CR. No other variable had an impact in OS.

Further improvements in outcome will require new treatment strategies to increase the CR rate, and especially to reduce the rates of rapid relapse.[14] Novel chemotherapy agents such as idarubicin[15] or new dosing schedules for conventional agents[16] appear to produce reasonably high CR rates, but with rapid leukemia recurence. Research to prolong remissions and obtain long-term DFS in the transplantation area for those lacking an HLA-identical sibling should focus on the use of alternative donor transplants with rapid access to the graft; cord blood transplants,[17] and, especially for adults, partially-mismatched related donor SCT[18,19] are potential areas of research. Matched unrelated BMT is of course another option, although it is probably of limited value to most of these patients at the present time due to the short duration of these CR and the time needed to find a suitable donor and perform the BMT. Although we did not address this issue in our study, a recent report from Minnesota found that only 13% of patients referred to their institution with ALL in second CR in whom an unrelated donor search was initiated eventually received a BMT.[20]

In conclusion, our intensive multi-agent salvage chemotherapy produces high CR rates in adult ALL with tolerable extrahematologic toxicity. However, durations of CR are still short and better post-remission therapies are needed. Allogeneic stem cell transplantation, either from a histocomptible sibling or from an alternative source, is an attractive alternative for these patients, and the procedure should be performed within four months from CR since remissions are usually short-lived.

Contributions and Acknowledgments

RM designed the study, was responsible for data management and prepared the manuscript. AAI performed the data analysis. MB and RG collaborated in patient care and data management. AAv and JFN performed the laboratory diagnoses and follow-up. JS is the head of the Division and participated in writing the paper. AS and SB collaborated in patient care and in preparation of the manuscript. ADA was the former chief of the Division and participated in the original design of the protocol.

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Disclosures

Conflict of interest: none.

Redundant publications: many patients' post-transplant outcomes were included in a previous manuscript (ref. #21).

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References

1. Bassan R, Lerede T, Barbui T. Strategies for the treatment of recurrent acute lymphoblastic leukemia in adults. Haematologica 1996; 81:20-36.
2. Welborn JL. Impact of reinduction regimens for relapsed and refractory acute lymphoblastic leukemia in adults. Am J Hematol 1994; 45:341-4.
3. Giona F, Testi AM, Annino L, et al. Treatment of primary refractory and relapsed acute lymphoblastic leukaemia in children and adults: the GIMEMA/AIEOP experience. Br J Haematol 1994; 86:55-61.
4. Ribera JM, Ortega JJ, Oriol A, et al. Late intensification chemotherapy has not improved the results of intensive chemotherapy in adult acute lymphoblastic leukemia. Results of a prospective multicenter ran-

domized trial (PETHEMA ALL-89). Spanish Society of Hematology. Haematologica 1998; 83:222-30.
5. Martino R, Brunet S, Sureda A, et al. Treatment of refractory and relapsed adult acute leukemia using a uniform chemotherapy protocol. Leuk Lymphoma 1993; 11:393-8.
6. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47:207-14.
7. García J, Puntí C, Picón M, et al. Bone marrow purging in acute lymphoblastic leukemia: biological and clinical features. J Hematother 1994; 3:203-11.
8. Giona F, Annino L, Rondelli R, et al. Treatment of adults with acute lymphoblastic leukaemia in first bone marrow relapse: results of the ALL R-87 protocol. Br J Haematol 1997; 97:896-903.
9. Testi AM, Moleti ML, Giona F, et al. A single high dose of idarubicin combined with high-dose ARA-C (MSKCC ALL-3 protocol) in adult and pediatric patients with acute lymphoblastic leukemia. Experience at the University "La Sapienza" of Rome. Haematologica 1997; 82:664-7.
10. Freund M, Diedrich H, Ganser A, et al. Treatment of relapsed or refractory adult acute lymphocytic leukemia. Cancer 1992; 69:709-16.
11. Ottmann OG, Hoelzer D. Do G-CSF and GM-CSF contribute to the management of acute lymphoblastic leuykemia? Leukemia 1996; 10:1111-6.
12. Torres Gómez A, Jimenez MA, Alvarez, et al. Optimal timing of granulocyte colony-stimulating factor (G-CSF) administration after bone marrow transplantation. A prospective randomized study. Ann Hematol 1995; 71:65-70.
13. Rowe JM. Treatment of acute myeloid leukemia with cytokines: Effect on duration of neutropenia and response to infections. Clin Infect Dis 1998; 26:1290-4.
14. Copelan EA, McGuire EA. The biology and treatment of acute lymphoblastic leukemia in adults. Blood 1995; 85:1151-67.
15. Weiss MA, Drullinsky P, Maslak P, Scheinberg D, Golde DW. A phase I trial of a single high dose of idarubicin combined with high-dose cytarabine as induction therapy in relapsed or refractory adult patients with acute lymphoblastic leukemia.Leukemia 1998; 12:865-8.
16. Koler CA, Kantarjian HM, Thomas D, et al. The hyper-CVAD regimen improves outcome of relapsed acute lymphoblastic leukemia. Leukemia 1997; 11:2039-44.
17. Gluckman E, Rocha V, Boyer-Chammard A, et al. Outcome of cord-blood transplantation from related and unrelated donors. N Engl J Med 1997; 337:373-81.
18. Fleming DR, Henslee-Downey PJ, Romond EH, et al. Allogeneic bone marrow transplantation with T cell-depleted partially matched related donors for advanced acute lymphoblastic leukemia in children and adults: a comparative matched cohort study. Bone Marrow Transplant 1996; 17:917-22.
19. Henslee-Downey P, Abhyankar SH, Parrish RS, et al. Use of partially mismatched related donors extends access to allogeneic marrow transplant. Blood 1997; 89:3864-72.
20. Davies SM, Ramsay NKC, Weisdorf DJ. Feasibility and timing of unrelated donor identification for patients with ALL. Bone Marrow Transplant 1996; 17:737-40.
21. Martino R, Bellido M, Brunet S, et al. Allogeneic or autologous stem cell transplantation following salvage chemotherapy for adults with refractory or relapsed acute lymphoblastic leukemia. Bone Marrow Transplant 1998; 21:1023-7.