Role of Chemotherapy and Allografting in the Treatment of Acute Lymphoblastic Leukemia

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Abstract

We report the clinical outcomes of 83 patients with acute lymphoblastic leukemia (median age, 46 years; range, 18-75 years) treated at our institution between 1999 and 2011. Treatment refers to clinical trials open for accrual at the time of diagnosis or to institutional guidelines. Upfront allografting was considered for younger high-risk patients. Seventy-eight of 83 (94%) patients achieved complete remission after induction, although 53% of them eventually relapsed. Forty of 70 patients younger than 61 years underwent allografting. The median follow-up was 7.4 years (range, 0.2-15.0 years). Overall, the 5-year overall survival (OS) and event-free survival (EFS) were 40% and 39%, respectively. In patients undergoing transplantation, OS and EFS at 5 years were both 53%, whereas in a nontransplantation setting, both OS and EFS were 35% at 5 years (P = .044 for both OS and EFS). By multivariate analysis, the independent predictors of OS and EFS were age and leukocytosis in the overall population and allografting in young patients.

Keywords

- Allogeneic stem cell transplantation;
- Leukocytosis;
- Targeted therapies;
- Tyrosine kinase inhibitors

Introduction

Adult acute lymphoid leukemia (ALL) is a rare disease with an estimated incidence of about 1 in 100,000.[1] With the current intense chemotherapy protocols, 90% of patients younger than 55 years achieve postinduction remission, but the majority invariably experience relapsed disease.[1] Postremission strategies have included prolonged chemotherapy, autografting, and allografting. More recently, the introduction of targeted therapy with tyrosine kinase inhibitors (TKIs)[2, 3, 4 and 5] and monoclonal antibodies[6, 7, 8 and 9] have changed the scenario of ALL treatment. Furthermore, persistence or reappearance of minimal residual disease (MRD) evaluated by molecular methods after induction may soon lead to risk-oriented treatment guidelines.[10]

The policy for the treatment of ALL at our institution has been that of enrolling patients in multicenter clinical trials and considering an allograft in first remission in young high-risk patients. The primary aim of this single-institution study was to compare the results of our policy with those reported in the current literature (http://ClinicalTrials.gov: NCT01785914).

Methods

Patients

Between December 1999 and December 2011, 88 consecutive adult patients were diagnosed with ALL at the Division of Hematology at Città della Salute e della Scienza Hospital, University of Torino, Torino, Italy according to standard criteria.[11] Five of 88 patients were excluded from the analysis because they received only supportive care owing to their poor clinical condition. All died shortly after diagnosis. Complete remission (CR), relapse, and refractory disease were defined according to published criteria.[12] Molecular analysis with qualitative and quantitative polymerase chain reaction has been performed since 2001, with minimal target sensitivity of 10^{-4}, as previously described.[13] Data were retrospectively and anonymously collected through the review of medical records. The study was approved by the Institutional Review Board of the Città della Salute e della Scienza Hospital of Torino, Torino, Italy according to the Declaration of Helsinki (http://ClinicalTrials.gov: NCT01785914). Patients were stratified by standard or high risk of progression by cytogenetic analysis, immunophenotyping, and presenting clinical features.[14]

Induction Chemotherapy

Patients were induced with chemotherapy regimens in prospective clinical trials active at the time of diagnosis or according to institutional guidelines for those not eligible for controlled trials. An allograft from a related or an unrelated donor was considered in all patients younger than 61 years in first complete remission (CR) if they were at high risk or in second CR if a standard risk of relapse existed.

Allografting

Myeloablative regimens consisted of cyclophosphamide/total body irradiation (TBI),[15] cyclophosphamide-busulfan, and thiotepa/busulfan/cyclophosphamide, whereas reduced-intensity conditioning regimens consisted of thiotepa/cyclophosphamide.[16] A low-dose total body irradiation–based nonmyeloablative regimen (200 cGy) was used in 2 patients with a high comorbidity score.[17] Acute and chronic graft-vs.-host disease (GVHD) was diagnosed and graded according to common criteria.[18 and 19]

Statistical Analysis

Primary end points were overall survival (OS) and event-free survival (EFS) from the time of diagnosis. OS was defined as the time from diagnosis to death from any cause, whereas EFS was defined as the time from diagnosis to disease progression/relapse or death from any cause, whichever occurred first. Patient characteristics were tested using the Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. OS and EFS were calculated using the Kaplan-Meier method and compared with the log-rank test; 2 landmark analyses for OS were performed at minimum and median times from diagnosis to allografting. For univariate analyses, OS and EFS were analyzed by the Cox proportional hazards model, comparing the 2 risk factors by the Wald test and calculating 95% confidence intervals (CIs). Univariate and multivariate analyses were carried out on the entire patient cohort and on patients younger than 61 years who were potential candidates for an allograft. Risk factors included age (> 60 years vs. 36-60 years vs. ≤ 35 years), year of diagnosis (2008-2011 vs. 2004-2007 vs. 2000-2003), leukocytosis (B lymphocytic acute leukemia [ALL], $> 30 \times 10^9$/L vs. $< 30 \times 10^9$/L; T lymphocytic acute leukemia [T-ALL], $> 100 \times 10^9$/L vs. $< 100 \times 10^9$/L), cytogenetic features and immunophenotyping at diagnosis (high vs. standard risk), presence of the *Bcr-Abl* rearrangement, allografting (yes vs. no), grade II/IV acute GVHD and chronic GVHD. Allografting and acute and chronic GVHD were treated as time-dependent variables. For patients undergoing transplantation, cumulative incidences of acute and chronic GVHD and nonrelapse mortality (NRM) were estimated by Gray competing risk regression models as previously described. [20] NRM was defined as death without previous relapse. Death without acute GVHD was considered a competing risk for acute GVHD, whereas death without chronic GVHD was considered a competing risk for chronic GVHD, and relapse was considered a competing risk for NRM. All *P* values were 2-sided at the conventional 5% significance level. Data were analyzed by IBM SPSS Statistics, version 21.0.0 (SPSS, Chicago, IL) and R 2.15.2 package cmprsk (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Study Population

Clinical characteristics of 83 evaluable patients are summarized in Table 1. Two HIV-positive patients receiving retroviral treatment were included. Overall by leukocytosis, cytogenetic analysis, and immunophenotyping,[1, 11 and 14] 57 of 83 (69%) patients were at high risk of progression, and 19 had a standard risk of progression. By cytogenetic analysis only, 36 patients had a high risk (Table 1). In the 57 high-risk patients, only 34 (60%) were eligible for an allograft as part of first-line treatment because of age or comorbidities, or both.

Table 1. Patient Characteristics

Sex (N)	
Male	36
Age (years)	
Median (range)	46 (18-75)
Phenotype (N)	
B-ALL	60
T-ALL	13
NK-ALL	2
Biphenotypic	4
Unknown[a]	4
WBC × 10^9/L (N)	
>30 B-ALL	21
>100 T-ALL	1
Unknown[a]	4
Cytogenetic Analysis (N)	
t(9;22)	22
t(4;11)	2
Complex (>5 aberrations)	4
Others	17
Normal	26
Unknown	12
Prognostic Stratification (N)[14]	
High risk	57
Standard risk	18
Unknown	8
Transplant patients	
N	40
Median age (range), years	41 (18-58)
Leukocytosis	12
Transplantation in CR1	34
Transplantation in CR2	5
Transplantation in progression	1
B-ALL	28
T-ALL	7
NK-ALL	2
Biphenotypic	2
Unknown	1

Abbreviations: B-ALL = B-lymphocytic acute lymphoblastic leukemia; CR = complete remission; NK-ALL = natural killer-acute lymphoblastic leukemia; T-ALL = T-lymphocytic acute lymphoblastic leukemia; WBC = white blood cell.

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Missing data.

Chemotherapy

All patients received induction and consolidation chemotherapy followed by either maintenance therapy or allografting. Seventy-nine of 83 (95%) patients were enrolled in prospective clinical trials, whereas 4 patients were treated according to institutional guidelines (Table 2).[10 and 21] All first-line treatments included steroids, vincristine, methotrexate, daunorubicin, and L-asparaginase. The 2 patients with HIV were treated with protocols 2 and 3 (Table 2); 1 of these patients required dose reduction because of liver toxicity.

Table 2. Treatment Protocols

Protocol	Prephase	Induction	Consolidation	Reinduction/ Intensification	Maintenance
Protocol 1 (n = 35) (2000-2006)		Prednisone Vincristine Daunorubicin L-asparaginase Methotrexate it	High-dose cytarabine Etoposide Cyclophosphamide	Vincristine Daunorubicin Cyclophosphamide Prednisone Methotrexate it Cranial irradiation	6-mercaptopurine Methotrexate
Protocol 2 (n = 6)	Dexamethasone Cyclophosphamide Methotrexate it	Dexamethasone Vincristine Daunorubicin L-asparaginase Cyclophosphamide Cytarabine 6-mercaptopurine Methotrexate it Cranial irradiation	Dexamethasone Vindesine Etoposide High-dose cytarabine High-dose methotrexate L-asparaginase 6-mercaptopurine Teniposide Cyclophosphamide Methotrexate it Cytarabine it Prednisone it	Prednisone Vindesine Doxorubicin Cyclophosphamide Cytarabine Thioguanine Methotrexate it Cytarabine it Prednisone it	Normal: 6-mercaptopurine methotrexate Intensified: cyclophosphamide Cytarabine Teniposide High-dose methotrexate L-asparaginase
Protocol 3 (n = 38) (2006-2011)	Cyclophosphamide Prednisone	Idarubicin Vincristine L-asparaginase Prednisone Methotrexate it Cytarabine it Prednisone it	Idarubicin Vincristine Cyclophosphamide Dexamethasone	High-dose cytarabine High-dose methotrexate Idarubicin Vincristine Prednisone	Cyclophosphamide Vincristine Prednisone 6-mercaptopurine Methotrexate

Abbreviation: it = intrathecal.

Transplant Preparative Regimens, Stem Cell Source, and GVHD

Overall, in the 70 patients younger than 61 years, 40 (57%) underwent an allograft procedure (Table 1) because of a high risk of relapse (n = 34), disease recurrence (n = 5), or disease refractory to first-line treatment (n = 1) (Table 1). Donors were HLA identical siblings (n = 22), unrelated (n = 15) or haploidentical siblings (n = 3). Conditioning regimens were myeloablative in the majority of cases (n = 38), and in 37 of 40 (93%) cases, granulocyte-colony stimulating factor–mobilized peripheral blood was the source of stem cells. Overall, 19 of 40 patients eventually died, and in 16 of the 19 patients, the cause of death was disease recurrence. The cumulative incidence of NRM was 2.5% at 1 year and 7.5% at both 3 and 5 years, whereas the relapse incidence was 17.5% and 40.5%, respectively. Cumulative incidences of grade II-IV acute and extensive chronic GVHD were 41.0% and 35.9%, respectively. No grade IV acute GVHD occurred. Only 2 patients underwent nonmyeloablative transplantation; both underwent transplantation in first CR but eventually died because of disease recurrence.

Disease Response

Overall, 78 of 83 (94%) patients achieved CR, and in 74 of 78 (95%) of them, CR was achieved within 4 weeks from induction. However, 41 of 78 (53%) eventually experienced relapse of disease. Five patients never achieved CR and died of disease progression at a median time of 3 months from diagnosis (range, < 1-8).

Disease-Specific Markers

Disease-specific molecular markers were identified in 34 of the 73 patients evaluated (47%). Twenty patients carried t(9;22) (Ph+ ALL) and 2 additional patients carried the *Bcr-Abl* rearrangement without t(9;22). Other markers included a monoclonal T-cell receptor in 7 patients, *MLLA-F4* in 2, *FR2-JH* in 2 and *FR3-JK* in 1 patient each. In 20 of 22 (90%) patients with the *Bcr/Abl* rearrangement diagnosed after 2002, treatments also included tyrosine kinase inhibitors (TKIs). Imatinib was given upfront in 17 of 20 patients (85%), and 6 of them later switched to dasatinib for persistent disease or molecular progression; 1 also received nilotinib and ponatinib. Four of 20 patients (20%) were treated with imatinib after induction because of persistence of MRD, and 1 patient also received dasatinib.

MRD and Allografting

Twenty of 40 patients who received an allograft had a molecular marker. MRD was evaluated in 19 of 20 patients during pretransplantation workup: 10 did not have MRD and 9 had MRD at the time of transplantation. During follow-up, 8 of 10 patients without MRD maintained a molecular response, whereas 3 of 9 patients with MRD achieved a status of no MRD after transplantation, and 4 still had MRD (data missing in 4 patients).

Clinical Outcomes

Overall Patient Population

After a median follow-up of 7.4 years (range, 0.2-15.0 years), 41% of the patients were alive, and 5-year OS and EFS were 40% and 39%, respectively (Figure 1). The 2 patients with HIV tolerated the treatment but eventually died of disease recurrence at 38 and 11 months, respectively. OS at 5 years was 15% in patients older than 60 years, 38% in those between 35 and 60 years, and 58% in patients younger than 35 years ($P = .001$), whereas 5-year EFS was 8%, 38%, and 58% ($P < .001$), respectively. OS and EFS at 5 years in patients with leukocytosis were 26% and 22%, respectively, and 51% and 51%, respectively, in those without leukocytosis ($P = .008$ and $P = .002$, respectively). Year of diagnosis and type of chemotherapy did not correlate with OS or EFS. Patients at high risk of relapse/progression by cytogenetic analysis showed a trend toward worse OS and EFS when compared with those at low risk (22 and 16 months, respectively, vs. not reached).

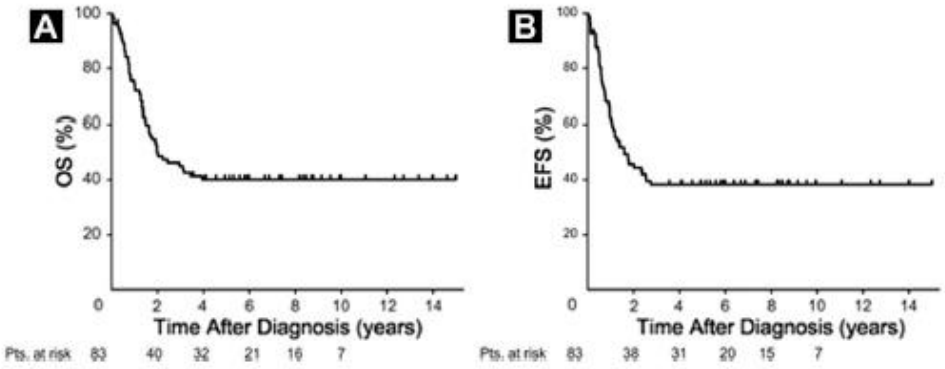

Figure 1. (**A**) Overall Survival (OS) and (**B**) Event-Free Survival (EFS) From Diagnosis of the Study Population

Univariate and multivariate analyses are shown in Table 3. By multivariate analysis, age and leukocytosis were statistically significant predictors of OS and EFS. Year of diagnosis was not associated with either OS (P = .656) or EFS (P = .636). The impact of high-risk cytogenetic results did not reach statistical significance.

Table 3. Univariate and Multivariate Analyses of the Entire Patient Cohort (N = 83)

	HR	95%CI	*P* Value
Univariate Analyses			
OS			
Age, years			.0002
35-60 vs. <35	1.80	0.88-3.72	.110
>60 vs. <35	4.63	1.95-10.98	.001
Year of Diagnosis			.449
2004-2007 vs. 2000-2003	0.76	0.37-1.54	.442
2008-2011 vs. 2000-2003	0.64	0.32-1.28	.207
Cytogenetic Analysis			
High risk vs. standard risk	1.44	0.76-2.71	.264
Leukocytosis			
Yes vs. no	2.26	1.21-4.19	.010
Immunophenotype			
High risk vs. standard risk	0.79	0.32-2.04	.631
Bcr-Abl			
Yes vs. no	0.96	0.50-1.86	.911
EFS			
Age			<.001
35-60 vs. <35	1.74	0.84-3.58	.134
>60 vs. <35	5.56	2.38-13.01	<.001
Year of Diagnosis			.456
2004-2007 vs. 2000-2003	0.79	0.39-1.58	.496
2008-2011 vs. 2000-2003	0.65	0.32-1.28	.210
Cytogenetic Analysis			
High risk vs. standard risk	1.52	0.81-2.85	.191
Leukocytosis			
Yes vs. no	2.53	1.38-4.65	.003
Immunophenotype			
High risk vs. standard risk	0.73	0.029-1.88	.517
Bcr_Abl			
Yes vs. no	1.10	0.58-2.09	.773
Multivariate Analyses			
OS			
Age, years			.034
35-60 vs. <35	2.04	0.92-4.55	.081
>60 vs. <35	3.68	1.37-9.88	.010
Leukocytosis			
Yes vs. no	1.98	1.01-3.87	.046
EFS			
Age, years			.013
35-60 vs. <35	1.89	0.85-4.20	.119
>60 vs. <35	4.25	1.61-11.19	.003
Leukocytosis			
Yes vs. no	2.08	1.08-4.00	.029

Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; OS = overall survival.

Patients Younger Than 61 Years of Age

Five-year OS and EFS were both 53% in patients undergoing transplantation and 35% in patients not undergoing transplantation (P = .044 for both OS and EFS). Median time from diagnosis to allografting was 6 months (range, 4-10 months). Landmark analysis at 4 months from diagnosis

showed a 5-year OS of 53% in 40 patients undergoing transplantation and of 36% in patients not undergoing transplantation (n = 28; *P* = .065), whereas landmark analysis at 6 months showed an OS of 53% and 38%, respectively (n = 40 and n = 26; *P* = .139).

At 5 years, both OS and EFS were 68% versus 50% (*P* = .543 and *P* = .459, respectively) in patients with MRD (n = 10) and patients without MDR (n = 9) before allografting. Of the 8 patients with a molecular marker who were not eligible for transplantation, all patients with MRD (n = 4) died, whereas all patients without MRD (n = 2) were alive at follow-up (data missing in 2 patients).

Univariate and multivariate analyses (Table 4) showed that allografting was the only variable correlated with longer OS and EFS. No impact of acute and chronic GVHD was observed.

Table 4. Univariate and Multivariate Analyses in Patients Younger Than 61 Years (n = 70)

	HR	95% CI	*P* Value
Univariate Analyses			
OS			
Age, years			
35-60 vs. <35	1.83	0.89-3.77	.102
Year of Diagnosis			.656
2004-2007 vs. 2000-2003	0.82	0.37-1.82	.619
2008-2011 vs. 2000-2003	0.69	0.31-1.52	.358
Cytogenetic Analysis			
High risk vs. standard risk	1.49	0.74-2.99	.259
Leukocytosis			
Yes vs. no	1.79	0.85-3.77	.126
Immunophenotype			
High risk vs. standard risk	0.72	0.25-2.06	.539
Bcr-Abl			
Yes vs. no	0.98	0.46-2.11	.956
hSCT[a]			
Yes vs. no	0.24	0.07-0.86	.028
Acute GVHD[a] **n = 39**			
Yes vs. no	0.60	0.05-7.47	.694
Chronic GVHD[a] **n = 39**			
Yes vs. no	0.01	0-1.13	.056
EFS			
Age, years			
35-60 vs. <35	1.76	0.85-3.62	.13
Year of Diagnosis			.636
2004-2007 vs. 2000-2003	0.79	0.36-1.77	.573
2008-2011 vs. 2000-2003	0.68	0.31-1.5	.682
Cytogenetic Analysis			
High risk vs. standard risk	1.48	0.74-2.98	.266
Leukocytosis			
Yes vs. no	1.88	0.89-3.96	.097
Immunophenotype			
High risk vs. standard risk	0.69	0.24-1.97	.487
Bcr-abl			
Yes vs. no	1.03	0.48-2.22	.935
hSCT[a]			
Yes vs. no	0.19	0.05-0.71	.013
Acute GVHD[a]			
Yes vs. no	1.80	0.13-24.72	.659
Chronic GVHD[a]			
Yes vs. no	0.11	0-2.84	.19
Multivariate Analyses			
OS			
Age, years			
35-60 vs. <35	1.80	0.87-3.72	.110
hSCT[a]			
Yes vs. no	0.53	0.28-1.01	.052

Abbreviations: CI = confidence interval; EFS = event-free survival; HR = hazard ratio; hSCT = hematopoietic stem cell transplantation; GVHD = graft-vs.-host disease; OS = overall survival.

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Treated as time-dependent variables.

Discussion

Current treatment of adult ALL represents an evolving paradigm. Our study summarized a 12-year experience in 83 consecutive patients with ALL diagnosed and treated at the Città della Salute e della Scienza Hospital in Torino, Italy. The aim was to compare the results of our "real-life" experience with that reported in the current literature, despite the limitation of the retrospective analysis.

With a median follow up of 7.4 years, OS at 5 years was 40%, which was similar to other reports.[1 and 22] Leukocytosis only was a strong predictor of survival. Patients with poor prognostic cytogenetic results showed a trend for a worse outcome, most likely because of the sample size and a larger proportion of high-risk patients (60%), by cytogenetic analysis, who underwent allografting. Similarly, the poor prognostic role of the *Bcr/Abl* rearrangement did not emerge.

Pediatric patients with ALL show better survival than adults.[1] Poorer outcomes in adults are multifactorial but are likely related to a higher incidence of adverse cytogenetic features and a lessened ability to tolerate intensive pediatric-inspired chemotherapy regimens. These factors carry even more weight in elderly patients who are rarely eligible for allografting.[23] However, 5-year OS has recently improved about 12% from the early 1980s to the early 2000s, especially in patients ≤ 60 years,[22] but our study period was too short to appreciate a significant difference. In our study, patients younger than 35 years gained a significant benefit regarding both OS and EFS, as confirmed by multivariate analyses ($P = .03$).

Several reports showed that high-risk patients are the most suitable candidates for allografting.[24 and 25] Most of our patients younger than 61 years (57%) underwent an allograft procedure. Although mostly prepared with myeloablative conditioning, NRM was extremely low. This finding may partially be explained by a high incidence of early relapse (17.5% at 1 year), transplantation in first CR (34 of 40 patients), and young median age (41 years). The incidence of acute and chronic GVHD (41.0% and 35.9%, respectively) was consistent with previously published data.[24, 25, 26 and 27] Allografting was correlated with a significant advantage regarding both OS and EFS compared with chemotherapy alone. Moreover, 2 landmark analyses at 4 and 6 months (minimum and median time from diagnosis to transplantation, respectively) suggested an advantage in patients undergoing transplantation, although the difference did not reach statistical significance. By multivariate analysis, allografting was confirmed as an independent predictor of outcome. Predictors of longer survival were age and leukocytosis in the whole study population.

Several points of interest have recently been raised in ALL treatment:

- MRD monitoring represents an independent risk factor,[10 and 28] and it may help to identify patients who would most benefit from an allograft.
- Reduced-intensity conditionings could broaden transplantation eligibility to older patients.[26 and 27]
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TKIs can be regarded as the first targeted therapy in ALL.[2, 3, 4 and 5] Their optimal role remains to be defined in both transplant-eligible and non–transplant-eligible patients.

- Monoclonal antibodies have been recently introduced: rituximab, which improved survival in CD20-positive ALL[6]; blinatumomab, a biallelic T cell engaging the CD3-CD19 monoclonal antibody, resulted in overall response rates of 40% to 50% in a refractory population with relapsed disease,[7 and 8] and inotuzubab ozogamicin, a CD33 monoclonal antibody bound to calicheamicin resulted in 55% CR in a similar setting.[9]

In conclusion, our "real-life" report suggests that our single-institution experience is similar to that reported by other groups and confirms the role of allografting. Hopefully, the introduction of novel targeted therapies as a bridge to transplantation or as maintenance in high-risk patients, or both, may better control the disease and improve transplantation outcomes, leading to a higher cure rate.

Clinical Practice Points

- Adult acute lymphoid leukemia is a rare disease.
- With the current intense chemotherapy protocols, 90% of patients younger than of 55 years achieve postinduction remission, but the majority invariably experience relapsed disease.
- Postremission strategies have included prolonged chemotherapy, autografting, and allografting.
- We reported the clinical outcomes of 83 patients with acute lymphoblastic leukemia, median age 46 years (range, 18-75 years) years, treated at a single institution between 1999 and 2011. Five additional patients were excluded because they died shortly after diagnosis before starting therapy.
- The aim was to compare the results of our "real-life" experience with that reported in the current literature. Most of the patients were at high risk of relapse and were enrolled in active clinical trials at the time of diagnosis.
- Overall, the 5-year survival was 40%. With the limitation of a retrospective analysis, our experience confirmed the impact of age and leukocytosis on patient survival in the whole population and the key role of allografting in patients younger than 61 years.

- The introduction of monitoring MRD and novel targeted therapies (such as TKIs and monoclonal antibodies) as a bridge to transplantation or as maintenance, or both, in high-risk patients may better control the disease and improve transplantation outcomes, leading to a higher cure rate.

Disclosure

The authors have stated that they have no conflicts of interest.

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B.B. and F.M. contributed to the initial conception and design of the study. L.G., B.B., E.A., S.D., C.D.C., A.B., M.F., C.D., L.B., E.C., R.B., M.B., U.V., M.F., and F.M. provided the study materials or patients. L.G., B.B., E.M., E.A., R.P., and F.M. collected or assembled (or both) or interpreted (or both) the data. R.P. conducted the statistical analyses. L.G., F.F., and B.B. wrote the manuscript. All authors gave final approval to the manuscript.

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