Original Study

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

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Abstract

Adult acute lymphoblastic leukemia (ALL) is rare. We summarize a single-center, 12-year experience of 88 consecutive patients treated in clinical trials or according to institutional guidelines. After a median follow-up of 7.4 years, median overall survival and event-free survival were 2.0 and 1.7 years, respectively. Overall, our "real-life" study confirmed the independent impact of allografting and leukocytosis on clinical outcomes.

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.

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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)[2-5] and monoclonal antibodies[6-9] 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).

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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.[18,19]

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,[1,11,14] 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.

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).[10,21] 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.

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