Original Study

Risk Factors Influencing Outcome of Acute Leukemia Patients Who Experience Relapse After Allogeneic Hematopoietic Stem-Cell Transplantation

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Abstract

In a study of 43 patients to assess the risk factors influencing relapse outcome after hematopoietic stem-cell transplantation in acute leukemia, older age and failure to experience complete remission (CR) after treatment were associated with inferior overall survival. Female sex, extramedullary relapse, and absence of postrelapse graft-versus-host disease (GVHD) were associated with lower CR; and absence of extramedullary relapse, treatment with donor lymphocyte infusion, and occurrence of postrelapse GVHD were associated with higher nonrelapse mortality.

Background: Prognosis of acute leukemia patients who experience relapse after hematopoietic stem-cell transplantation (HSCT) remains poor. Identifying risk factors influencing outcome of these patients is essential. **Patients and Methods:** Follow-up of 234 acute leukemia patients who underwent allogeneic HSCT from matched related donor was performed for occurrence of posttransplantation relapse. Statuses of remission and survival were assessed at 6 months after treatment of relapse. Analysis of risk factors influencing postrelapse overall survival (prOS), complete remission (CR), and nonrelapse mortality (NRM) was carried out. **Results:** Posttransplantation relapse occurred in 43 patients (17.9%). After treatment, 11 patients (25.6%) experienced postrelapse remission, the prOS rate was 20.9% (9 patients), and the NRM rate was 25.6% (11 patients). Older age ($P = .007$) and failure to experience remission after relapse treatment ($P = .027$) were associated with lower prOS in multivariate analysis. Female sex ($P = .027$), posttransplantation extramedullary relapse ($P = .001$), and absence of postrelapse graft-versus-host disease $P = .025$) were associated with lower CR rate. Also, presence of extramedullary relapse ($P = .011$) was associated with lower risk of NRM whereas treatment of posttransplantation relapse with donor lymphocyte infusion with or without chemotherapy ($P = .002$) and occurrence of postrelapse graft-versus-host disease ($P = .025$) were associated with higher risk of NRM. **Conclusion:** Survival of acute leukemia patients who experience relapse after allogeneic HSCT is poor, especially in elderly patients and those who do not experience remission after relapse treatment.

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Introduction

Allogeneic hematopoietic stem-cell transplantation (HSCT) is one of the most effective treatments for hematologic malignancies, helping the patient to experience long-term remission and potentially curing many patients.[1] Although significant progress has been made in allogeneic HSCT, posttransplantation relapse remains one of the most important causes of transplant failure.[1] The classical approach to controlling disease by HSCT relied on high-intensity conditioning and modulation of the balance between the linked graft-versus-host disease (GVHD)/graft-versus-leukemia (GVL) effect and relapse by varying T-lymphocyte immunosuppression.[2] GVL response has been observed to be most potent in patients with chronic myeloid leukemia and, although present, is not as robust in patients with acute myeloid leukemia (AML) or acute lymphoblastic leukemia (ALL).[3]

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Unfortunately, treatment options for posttransplantation relapse are still limited, and outcomes are poor.[4] Identifying prognostic factors of post-HSCT relapsed patient survival time is important not only because it enables the physicians to detect the factors whose changes affect patients' outcome but also because it helps them to make the best decision about patient treatment.[5] Recent studies described the outcomes in patients with acute leukemia who experienced relapse after reduced-intensity conditioning (RIC) HSCT,[6-8] but few studies have identified the factors that influence survival after relapse across multiple transplantation types.[9] Given the need for a better understanding of outcome of post-HSCT relapse of acute leukemia patients, we performed an analysis to identify pretransplantation, posttransplantation, and postrelapse risk factors influencing posttransplantation relapse outcome.

Patients and Methods

Patients

This study included 234 adult acute leukemia patients who underwent peripheral blood allogeneic HSCT from a matched related donor from January 2010 to June 2017. The hematopoietic cell transplantation comorbidity index was used to categorize patients according to number of comorbidities.[10] The mean age of patients was 33.11 years (range, 16-63 years). The study included 122 men (52.1%) and 112 women (47.9%). One hundred forty-one patients (60.3%) had AML, 79 (33.8%) had ALL, and 14 (6%) had biphenotypic acute leukemia. Twenty-four patients (10.3%) had hematologic disease before presentation with acute leukemia. Thirty-four patients (14.5%) had extramedullary disease at presentation. The Southwest Oncology Group cytogenetic risk classification was used to categorize patients into favorable-, intermediate-, and poor-risk groups.[11,12] Accordingly, 19 patients (8.1%) had favorable-risk cytogenetics at presentation, 181 (77.4%) had intermediate-risk cytogenetics, and 34 (14.5%) had poor-risk cytogenetics.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethical committee of Faculty of Medicine, Ain Shams University, and with the 1975 Helsinki Declaration as revised in 1983. Informed consent was obtained from all individual participants included in the study.

Transplantation Procedures and Follow-up

Patients were admitted in isolated single rooms ventilated with a high-efficiency particulate air filtration system. One hundred sixty-six patients (70.9%) were transplanted in first complete remission and 68 (29.1%) were transplanted after first complete remission. Patients received myeloablative conditioning, except 11 patients (4.7%) who received RIC. All patients received granulocyte-colony stimulating factor starting from posttransplantation day 6 until 3 days after neutrophil engraftment. GVHD prophylaxis was with methotrexate and ciclosporin. Ciclosporin was substituted by mycophenolate mofetil in case of toxicity. Patients were monitored for occurrence of relapse for 2 years after HSCT. Extramedullary relapses were proven by biopsy or cerebrospinal fluid analysis.

Treatment of Patients With Relapse and Follow-up

All patients with relapsed disease who were receiving immunosuppressive therapy immediately stopped it. Donor lymphocyte infusion (DLI) was prescribed to patients without significant GVHD, with $\geq$ 20% donor chimerism. Otherwise, patients were subjected to salvage chemotherapy (FLAG-Ida protocol consisting of granulocyte-colony stimulating factor has been provided subcutaneously from day -1 to day $+5$, fludarabine 30 mg/m^2 provided intravenously from day $+1$ to day $+5$, cytarabine 2 gm/m^2 provided intravenously from day $+1$ to day $+5$, and idarubicin 8 mg/m^2 provided intravenously days 3, 4, and 5). Patients refusing treatment were given best supportive care. Patients were followed up for a period of 6 months after treatment of relapse for occurrence of subsequent remission and survival. Remission assessment in case of extramedullary relapse was performed using clinical examination, imaging studies, and/or cerebrospinal fluid analysis, depending on the site of relapse.

Definitions and Statistical Methods

Postrelapse overall survival (prOS) was defined as the time from randomization to treatment of relapse to the time of death from any cause. CR rate was defined as number of patients with normocellular bone marrow with $<$ 5% blasts along with the absence of blasts in the peripheral blood and absence of extramedullary disease. Nonrelapse mortality (NRM) was defined as death from toxicities related to therapy without disease recurrence. In patients who died without a confirmed hematologic remission within 30 days from initiation of relapse treatment, the cause of death was defined as NRM. In patients who died without a confirmed hematologic remission after 30 days, the cause of death was defined as refractory disease.[13] Patients with no reported event at the time of analysis were censored at the most recent assessment date. Descriptive statistical analysis of variables was done (mean, range, number, and percentage), and they were compared by the independent-sample t test (for continuous variables) and the chi-square test (for categorical variables). Survival probabilities were calculated by the Kaplan-Meier method. Multivariate analysis of variables influencing prOS was performed by the Cox proportional hazards model. Statistical significance was determined at the .05 level. All P values were 2 sided. SPSS for Windows 17.0 (IBM SPSS, Chicago, IL) was used for data entry and analysis.

Results

Posttransplantation Relapse Assessment and Treatment

Forty-three patients (18.4%) experienced relapse after transplantation; 25 (58.1%) had bone marrow relapse, 13 (30.2%) had bone marrow relapse associated with extramedullary relapse, and 5 (11.6%) had lone extramedullary relapse. The characteristics of patients who experienced relapse are listed in Table 1. Regarding karyotyping of patients with relapse in the AML group, 6 (14%) had t(8;21), 2 (4.7%) had t(16;16), 15 (34.9%) had normal karyotype, 2 (4.7%) had $+8$, 1 (2.3%) had -7, and 1 (2.3%) had complex karyotype. Of the 13 patients with relapse in the ALL group, 2 (4.7%) had hyperdiploidy, 4 (9.3%) had normal karyotype, 5 (11.6%) had t(9;22), and 2 (4.7%) had t(4;11). Regarding the biphenotypic acute leukemia group, 2 (4.7%) had t(9;22) and 1 (2.3%) had complex karyotype. Thirteen patients (30.2%) received DLI with or without chemotherapy, 25 (58.1%) received salvage chemotherapy, and 5 (11.6%) did not receive treatment or withdrew immunosuppressive treatment either because of refusal of intensive treatment (2 patients) or because they died before treatment initiation (3 patients).