Prognosis of Patients With *de novo* Acute Myeloid Leukemia Resistant to Initial Induction Chemotherapy

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ABSTRACT

Background: Initial induction chemotherapy is critical for patients with newly diagnosed *de novo* acute myeloid leukemia (AML). The aim of the present study was to analyze the factors affecting the outcome of patients with AML who failed to initial chemotherapy.

Materials and Methods: We retrospectively analyzed clinical data of 311 adults with *de novo* AML.

Results: Compared with 179 patients showing complete remission (CR), 132 patients who failed to achieve CR were older with poorer prognostic stratification, higher proportion of FLT3-ITD mutations, higher expression rates of CD9, lower expression rates of cMPO and CD64 and poorer overall survival (OS). The 2-year OS rate of the non-CR groups was inferior to that of the CR groups (28.3% versus 53.3%, $P < 0.001$). However, there was no dramatic difference in 2-year OS rate between initial and reinduction chemotherapy if patients achieved a same remission status. The 2-year OS rate significantly improved following allogeneic hematopoietic cell transplant in patients who failed to initial treatment. The survival of patients with similar remission status was affected by FLT3-ITD mutation instead of $CD9^{+}$ expression.

Conclusions: Initial induction failure or poorer prognostic stratification seriously affected the survival of patients with *de novo* AML. The allogeneic hematopoietic cell transplant is an alternative strategy to improve the survival of patients resistant to initial treatment.

Key Indexing Terms: Acute myeloid leukemia; Initial induction failure; Prognosis; Immunophenotype. **[Am J Med Sci 2016;351(5):473–479.]**

INTRODUCTION

Acute myeloid leukemia (AML) is a hematopoietic stem cell disorder. The AML is characterized by a block in differentiation of hematopoiesis, which results in overproliferation of a clonal population of blasts.[1] The AML treatment consists of induction chemotherapy and postremission therapy to debulk the disease until the residual leukemia was eliminated and hematopoiesis was restored.[2] After initial induction chemotherapy with cytarabine and anthracyclines, approximately 60–80% of younger patients with newly diagnosed AML achieve complete remission (CR) using standard therapy. Only 40–55% of elderly patients achieve CR.[1] However, a sizable proportion of patients, approximately 20–25%, fail to achieve initial remission with protocol-directed therapy.[3] A growing number of studies described the relevant factors and outcomes associated with initial induction failure. Othus et al[3] analyzed 150 patients with newly diagnosed AML who did not achieve a remission and found the 4-year survival rate of 23%. Among the 64 patients who received an allogeneic hematopoietic stem cell transplantation (allo-HSCT), the 4-year survival rate increased to 48%. These results suggest that allo-HSCT is an important measure of the initial induction failure of AML.

In the current retrospective study, we evaluated 311 patients with *de novo* AML (other than M3 type) who were treated with initial induction chemotherapy from January 2008-September 2014. In all, 132 patients failed to achieve CR. We investigated the differences in diagnosis and outcome of non-CR patients compared with cases who achieved CR following initial chemotherapy. The results are valuable on more accurately predicting therapeutic effect and more reasonablely choosing strategies for improving the outcomes of patients with *de novo* AML with initial induction failure.

MATERIALS AND METHODS

Patients' Characteristics

Between January 2008 and September 2014, a total of 311 hospitalized patients with newly diagnosed *de novo* AML (other than M3 subtypes) were treated at Tongji Hospital, Wuhan, China. All patients received initial chemotherapy and were available for follow-up evaluation. The diagnosis of AML was based on the WHO 2008 criteria for AML.[4] The percentage of blasts in bone marrow (BM) or peripheral blood smears took at initial diagnosis was greater than 20%. In patients with recurrent genetic abnormalities including t(8; 21)

(q22; q22); inv(16) (p13; 1q22) and t(9; 11) (p22; q23) may have a blast percentage less than 20%.

Karyotype Analysis

Karyotype analysis was performed on samples from the diagnostic BM according to standard methods and International System for Human Cytogenetic Nomenclature guidelines.[5] At least 20 metaphases were examined to identify clonal abnormalities. According to the National Comprehensive Cancer Network guidelines of AML, the favorable-risk cytogenetic group was characterized with inv16 or t (16; 16), t (8; 21). Patients with -5/5q-, -7/7q-, t (6, 9), t (9, 22), inv (3), t (3; 3), 11q23-non t (9; 11) or complex aberrations (>3 independent clonal chromosomal abnormalities) were categorized as poor risk. Patients with +8, t (9; 11) normal or other non-defined cytogenetics were defined as intermediate-risk group.[6] Mononuclear cells from BM or blood were enriched, then genomic and total RNA were extracted for fusion gene screening and molecular mutant analysis.

IMMUNOPHENOTYPIC ANALYSIS

The BM or peripheral blood samples were processed using a whole-blood lysis technique. Immunophenotyping was performed by multiparameter flow cytometry (EPICSTM XL-MCL, Beckman Coulter, Fullerton, CA) with fluorochrome-conjugated antibodies directed toward CD9, CD64, cMPO, CD33, CD34, CD117, HLA-DR, CD19, CD14, CD7, CD15, CD16, CD11b, CD11c and CD36, and an autofluorescent negative control using an EPICS XL-MCL flow cytometer (Beckman Coulter, Fullerton, CA). The leukemic blasts were gated according to dim CD45 staining and low-side scatter. For each sample, 10,000 list-mode events were recorded in the blast gate. Most antigens were categorized as positively expressed when detected on over 20% of all blasts, but for leukemic cell intracellular antigens, such as cMPO, a threshold of 10% was applied.[7,8]

Induction Regimens and Response Criteria

Initial induction chemotherapy included (1) "3 + 7" regimen with standard-dose cytarabine and daunorubicin[9] or idarubicin or homoharringtonine and (2) CAG regimen (low-dose cytarabine [10 mg/m^2 per 12 hours, days 1-14], aclarubicin [5-7 mg/m^2 per day, days 1-8] and granulocyte colony-stimulating factor [200 μg/m^2 per day, days 1-14]), or modified CHG regimen (aclarubicin was replaced with 1 mg/m^2 homoharringtonine per day, days 1-8].[10,11] The 2 regimens were mainly used for elderly patients or for those intolerant to "3 + 7" regimen or hypocellular leukemia. If the above-mentioned protocol-directed regimens were strictly followed, it was defined as an adequate chemotherapy. Otherwise, it was defined as an inadequate chemotherapy.

The CR was defined by the presence of normal cellular BM with less than 5% blasts along with a neutrophil count >1 × 10^9/L, peripheral blood platelet count ≥100 × 10^9/L, no blasts with *Auer* rods or persistence of extramedullary disease and the patient was independent of transfusion. Patients failing to achieve a complete response are considered as induction failures. Follow-up was until December 31, 2014. Median follow-up time for survival was 11 months (range: 1/–82 months). Overall survival (OS) was defined as the period since the time of first diagnosis to death or censored alive on the last known date.

Statistical Analysis

Clinical characteristics were described in numbers and frequency of qualitative variables, the median for quantitative factors. Qualitative parameters were evaluated by X^2 test or Fisher's exact test. Quantitative parameters were evaluated by nonparametric *U* test for independent samples. The 2-year OS rates were calculated by Kaplan-Meier method, and were compared using a log-rank test. Cox regression analysis was used to assess univariate and multivariate analyses of the factors affecting the OS. Two-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS for Windows 20.0. Graphpad Prism 5.0 was used for plotting graphs.

RESULTS

Patients' Characteristics

After initial induction chemotherapy, 132 patients (42.44%) failed to achieve CR and were classified as non-CR group. The remainder of 179 patients (57.56%) was classified into CR group. Next, we compared the demographic differences of the 2 groups, which are presented in Table 1. The average age was higher in non-CR group than in CR group ($P = 0.001$). The proportion of older patients (≥60 years) was 15.2% (20 of 132) in non-CR group, and only 8.9% (16 of 179) in CR group. The percentage of BM blasts was higher in non-CR group than in CR group ($P = 0.023$). No statistical differences in hemoglobin levels, white blood cells (WBCs), platelet counts or lactate dehydrogenase (LDH) levels were seen between the 2 groups ($P > 0.05$). Disparities in AML subtypes distribution were significant between the 2 groups ($P = 0.013$). A total of 40 patients received an inadequate initial chemotherapy due to poor tolerance. Most of them (36 of 40) did not achieve CR. Reinduction chemotherapy was administered to 80.3% (106 of 132) cases in the non-CR group. In all, 68 patients were available for treatment evaluation. The overall response rate was 63.2% (43 per 68).

Prognostic Stratification, Gene Mutation and Immunophenotyping

The difference of prognostic stratification in 2 groups was obvious ($P = 0.002$). Compared with patients showing CR status, patients with non-CR status had