SOHO Supplement 2015

Relapsed Acute Myeloid Leukemia: Need for Innovative Treatment Strategies to Improve Outcome

Talha Badar, Farhad Ravandi

Abstract

Relapse remains a major obstacle in improving outcomes of patients with AML. Increased understanding of the molecular aberrations leading to the pathogenesis of AML is providing us with several target specific drugs. Future strategies combining chemotherapy with these drugs are likely to lead to better outcomes.

Relapse continues to be a major hurdle in achieving cure in patients with acute myeloid leukemia (AML). The outcome after relapse is not uniform in all patients with AML and is dependent on several prognostic variables, including age, cytogenetics at initial diagnosis, duration of first complete remission, whether an allogeneic stem cell transplant was performed during first complete remission, and the presence of a number of molecular aberrations. Despite extensive research over the past several decades, there is no standard of care for treating patients with relapsed AML. This is possibly due to the accrual of patients with widely different disease profiles in most trials for relapsed AML. With increasing insights into the disease biology based on identification of pathogenic and aberrant molecular and cellular pathways, novel therapeutic strategies are emerging. Hopefully in the near future, we can improve the outcome of patients with relapsed AML with treatment strategies based on identification of specific targets and methods to overcome these aberrant processes.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. S1, S104-8
Keywords: AML, Molecular targets, Novel agents, Outcome, Relapse

Introduction

The therapeutic approach for adult patients with acute myeloid leukemia (AML) has not changed considerably over the last several decades, for which anthracycline and cytarabine combination regimens have remained the standard of care.[1] Improvement in outcome observed over the last few decades is mainly attributed to improvements in supportive care and higher success rates in treating patients with favorable-risk AML, including those with core binding factor leukemias and acute promyelocytic leukemia.[2] However, the extent of improvement in survival decreases with age.[2-4] The 5-year survival in elderly patients (aged $\geq$ 60 years) with AML remains at less than 10% to 20%.

Relapse continues to be the major hurdle to achieve cure after obtaining remission with induction chemotherapy. Rowe and colleagues[5] reported survival outcome after relapse in patients with AML treated on several frontline studies conducted by the Eastern Cooperative Oncology Group (ECOG). In patients aged less than 55 years, 68% (1150/1699) achieved complete remission (CR) after induction chemotherapy, among them 402 (35%) relapsed and had a median overall survival (OS) of 6.4 months with 5-year survival of only 11%. The relapse rate was higher and survival was even poorer in patients aged more than 55 years; 237 patients (65%) relapsed, with median OS of 4.7 months and 5-year survival of only 6%. In the same analysis, outcomes of patient treated in the US intergroup study were slightly better. Patients aged less than 55 years had a median OS from the time of relapse of 6.6, 5.2, and 8 months after allogeneic transplant, autologous transplant, and consolidation chemotherapy, respectively. Five-year OS was 18%, 0%, and 0%, respectively, for the 3 groups. The dismal prognosis associated with relapsed AML merits the development of novel treatment strategies to improve the outcomes.

Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX

Submitted: Mar 18, 2015; Accepted: Mar 18, 2015; Epub: Mar 27, 2015

Address for correspondence: Farhad Ravandi, MD, Department of Leukemia, UT MD Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX 77030
E-mail contact: fravandi@mdanderson.org

Prognostic Factors Predicting Outcome

Several factors have been identified that influence the outcome after first relapse. These include age, duration of first complete remission (CR1), cytogenetics at initial diagnosis, and whether the

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.03.012

patient had an allogeneic stem cell transplant (alloSCT) in CR1.[6-8] Keating and colleagues[6] reported that older patients with relapsed AML had a lower probability of achieving a second remission and were more likely to be resistant to therapy. Among the patients aged more than 65 years, only 14% achieved a second CR (CR2) and 47% were resistant to therapy. Estey et al[7] reported that the duration of CR1 is an important predictor of response to salvage therapy and survival. Among the patients who relapsed within 1 year after achieving CR1, 14% achieved a CR2 compared with 73% of patients who relapsed after 2 years of continuous remission. Additional data suggest that the patients with CR1 duration of less than 1 year have survival rates that are equivalent whether they receive high-dose cytarabine-based chemotherapy regimens or investigational agents on phase 1 clinical trials, as first salvage.[9] The reasons for these comparable outcomes were high treatment-related mortality during reinduction and shorter remission duration in CR2 using traditional chemotherapy. In contrast, if CR1 duration is between 1 and 2 years, a high-dose cytarabine-based regimen does improve survival when compared with investigational agents.

In another study, the outcome of 1540 patients was evaluated who were treated in the HOVON/SAKK trials between 1987 and 2001.[8] In this analysis, 60% of patients (667/1108) relapsed after achieving CR with induction chemotherapy, and on multivariate analysis age, CR1 duration, cytogenetics at diagnosis, and history of alloSCT were important predictors of outcome. Furthermore, using these prognostic factors, patients were divided into 3 groups: favorable, intermediate, and poor risk. The 5-year survival was 46%, 18%, and 4% in the favorable-, intermediate-, and poor-risk groups, respectively ($P \leq .001$). Of note, approximately two thirds of the patients were identified as poor risk. Similar prognostic factors were identified by Kurosawa et al[10] in a retrospective analysis from a Japanese population of patients with AML. Among the 1535 patients treated with chemotherapy alone, 66% relapsed after achieving CR1 and only 30% of patients were alive 3 years after relapse. In multivariate analysis achievement of CR2, salvage alloSCT and relapse-free duration of 1 year were independent prognostic factors.

Role of Minimal Residual Disease in Predicting Relapse

With the development of highly advanced techniques for the detection of minimal residual disease (MRD) in leukemia, eradication of MRD is gaining importance.[11,12] Several studies have demonstrated that persistence of MRD is associated with adverse outcome.[13-15] This certainly has influenced our concept of chemosensitive and chemoresistant disease, and our treatment approach. In acute promyelocytic leukemia, we have learned that patients who are persistently positive for *PML-RARA* fusion transcripts by polymerase chain reaction analysis after consolidation therapy have a high risk of relapse and should be treated preemptively with arsenic trioxide.[16] Freeman et al[14] prospectively assessed MRD by multiparameter flow cytometry (MFC-MRD) in 892 patients treated in the UK National Cancer Research Institute AML 16 trial. Patients who remained MFC-MRD positive after achieving CR had a higher risk of early relapse, with a median time to relapse of 8.5 months compared with 17.1 months in patients who became MFC-MRD negative. In multivariable analysis, MRD status after cycle 1 independently predicted survival. Several molecular markers have been identified for monitoring MRD in AML, including core binding factor leukemia translocation fusion transcripts, Wilms' tumor gene expression, and nucleophosmin-1 mutant level.[12,13,17] The data clearly warrant the establishment of time points for persistent MRD and development of effective and nontoxic post-remission treatment strategies.

Salvage Therapy

The dose of cytarabine used in salvage regimens for relapsed AML is of key importance. Kern et al[18] evaluated the response to 2 different dose regimens of cytarabine with mitoxantrone in a population of patients with refractory AML or in first relapse. Patients aged less than 60 years received mitoxantrone with cytarabine doses of 3.0 g/m^2 or 1.0 g/m^2 per dose, and patients aged more than 60 years received cytarabine doses of 1.0 g/m^2 or 0.5 g/m^2 per dose. Higher doses of cytarabine in the younger patients decreased the proportion of nonresponders (12% vs. 31%; $P = .01$) but also resulted in increased early death (32% vs. 17%). This led to only a slight improvement in CR rate (52% vs. 45%). Likewise, in patients aged more than 60 years, a higher rate of nonresponders was observed in the lower dose group (26% vs. 16%), but early death occurred more frequently with the higher doses of cytarabine (36% vs. 26%). Therefore, although higher doses of cytarabine have been associated with a better antileukemic activity, this has not been translated to a significant improvement in CR rate because of the higher early mortality. With significant improvement in supportive care and treatment of infectious complication over the years, a high dose of cytarabine has the potential to improve the response rate and long-term outcomes, particularly in younger patients.

Ravandi et al[19] reported the characteristics of a patient refractory to 1 cycle of high-dose cytarabine induction. Refractory patients were older (median age, 59 vs. 56 years; $P \leq .001$) and more likely to have unfavorable cytogenetics (35% vs. 15%, $P \leq .001$), antecedent hematologic disorder (58% vs. 34%, $P \leq .001$), therapy-related AML (19% vs. 14%, $P = .03$), and a high white blood cell count ($P = .04$). Among 285 patients with primary refractory disease, only 18% achieved a CR with salvage therapy and had a median survival of 3.8 months. In contrast, Rowe and colleagues[20] reported data in patients treated in 6 AML studies conducted by the ECOG and reported that the survival outcome was similar in patients who achieve CR after 1 or 2 cycles of "standard dose" induction chemotherapy.

Over the last several decades, it has become clear that AML is a heterogeneous disease and response to chemotherapy is not uniformly similar. The outcome can vary considerably depending on the disease profile of an individual patient. We can broadly categorize patients as having an inherently chemosensitive or inherently chemoresistant disease. Patients with chemosensitive disease are more likely to respond to cytarabine, and anthracycline-based chemotherapy and dose escalation if tolerated may result in improved outcomes. This has been well described in patients with core binding factor leukemias, in whom high-dose cytarabine consolidation results in improved survival.[21] Likewise, younger patients without adverse risk cytogenetics benefit from daunorubicin dose escalation.[22] Patients with chemoresistant disease have poor-risk cytogenetics, or secondary or FMS-like tyrosine kinase 3 (*FLT3*) mutated AML, in whom dose intensification has not