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4

Relapsed acute myeloid leukemia: Why is there no standard of care?

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Relapse after achieving a prior response remains one of the most important obstacles to improving the outcome of patients with acute myeloid leukemia (AML). Although overall, the majority of patients with disease relapse do poorly, this is by no means uniform and a number of predictors of outcome have been identified. Previously, most trials of investigational agents in the setting of disease relapse in AML have accrued a wide range of patients with widely different patient and disease characteristics. With increased understanding of the biology of the neoplastic change in AML, and better identification of disease subsets based on their molecular characterization, target-specific novel agents are being developed that will hopefully lead to better strategies, not only for treating relapsed disease, but also for the initial induction treatment.

Introduction

The treatment of adult patients with acute myeloid leukemia (AML) has not changed significantly over the past several decades, with cytarabine and anthracyclines remaining the most important agents used in the induction regimens M [1]. The modest improvement in the survival of patients over the past several decades can be attributed, at least in part, to improvements in supportive care, including better blood product support and better control of infections, as well as higher success in treating patients with better risk disease, such as those with core binding factor leukemias and acute

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promyelocytic leukemia [2]. This progress has been limited particularly in older patients who constitute the majority of the cases (Fig. 1) [2].

Relapse continues to remain a major obstacle to achieving cure after successful initial therapy of patients with AML. Rowe et al. reported that among 362 patients over the age of 55 years who achieved a complete remission (CR) after the initial induction therapy in various frontline studies conducted by the Eastern Cooperative Oncology Group (ECOG), 237 (65%) relapsed and had a median survival of 4.7 months with only 6% of patients remaining alive at 5 years [3]. In the same report, the outcome of patients treated on the study E3489 who relapsed was better for patients who did undergo an allogeneic stem cell transplant in second CR compared to those who received continued chemotherapy alone (5-year survival 18% vs. 0%, respectively).

Outcome predictors

A number of predictors of outcome in first relapse have been described. Keating et al. demonstrated clearly that age per se is an important predictor of response to first salvage regimen [4]. Advancing age decreases the proportion of patients achieving CR and increases resistant disease [4]. Estey et al. demonstrated that the duration of the first remission was an important predictor of survival in first relapse [5]. Patients whose first CR duration was less than 1 year had similar outcome whether they received high-dose cytarabine-based regimens or investigational agents on phase 1 trials, whereas those with a first CR duration longer than a year had significantly better outcomes when treated with cytarabine-based regimens [6].

Breems et al. evaluated the outcomes of 1540 patients treated on the HOVON/SAKK trials between 1987 and 2001. Six hundred sixty-seven (60%) of 1108 patients who had achieved CR and were alive, relapsed [7]. Using multivariate analysis, they identified four important prognostic indicators for survival, including cytogenetics at initial diagnosis, age at relapse, duration of first CR (CR1), and whether the patients had undergone an allogeneic stem cell transplant in CR1 before relapsing [7].

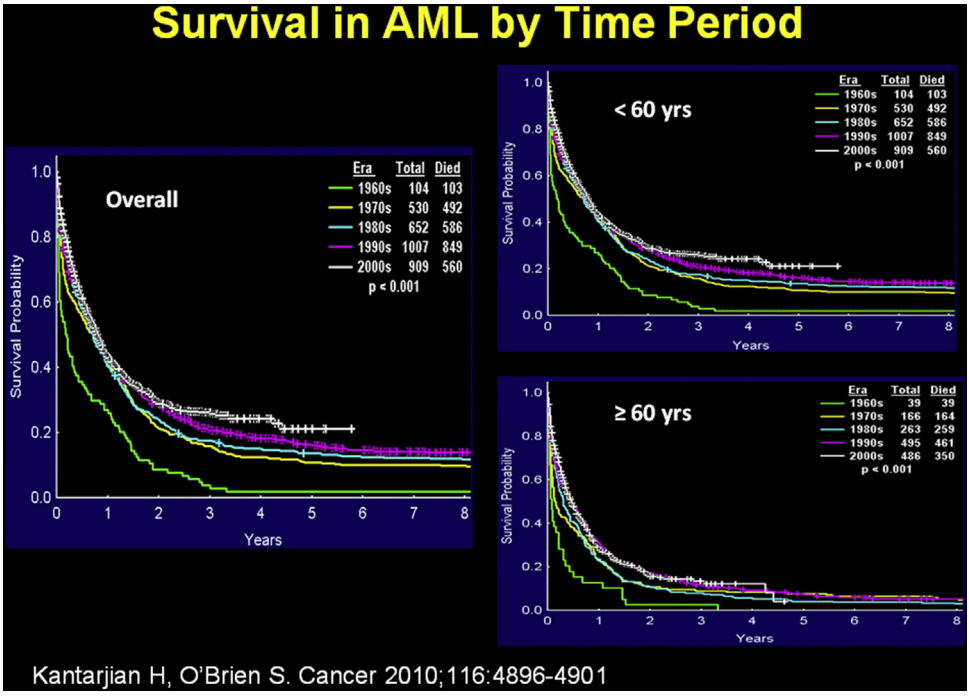

Fig. 1. Survival in AML by time period. From: Kantarjian H, O'Brien S. Questions regarding frontline therapy of acute myeloid leukemia. Cancer 2010; 116:4896–4901. Reprinted with permission of John Wiley and Sons. Copyright © 2010 American Cancer Society.