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Do cytogenetics affect the post-remission strategy for older patients with AML in CR1?

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A B S T R A C T

Data have shown that intensified cytarabine in consolidation for treatment of acute myeloid leukemia (AML) does not equally benefit patients older than 60 years, and older patients experience significantly more neurotoxicity than younger patients. In addition, older patients are more likely to have abnormal or unfavorable cytogenetics, which also tend to confer limited efficacy with intensified cytarabine. This poses a treatment dilemma as to the best post remission therapy to treat older patients. This review explores some of the consolidation treatment strategies and options available for the older AML patient.

1. Introduction

When considering the topic of this paper, most physicians will agree that acute myeloid leukemia (AML) biology predicts response and relapse after standard intensive therapy, particularly for younger patients. National Comprehensive Cancer (NCCN) guidelines and updates from European LeukemiaNet (ELN) 2017 identify cytogenetic risk groups and classify them into better (favorable) risk, intermediate risk, or poor (adverse) risk, sometimes incorporating molecular abnormalities into the classifications (Table 1) [1,2]. Older data using Cancer and Leukemia Group B (CALGB) criteria demonstrate that relapse is strongly correlated with a patient's cytogenetic risk [3]. Similarly, even earlier CALGB data showed that intensified cytarabine in consolidation, which is primarily the focus of this paper, improves remission duration in patients with more favorable cytogenetics, such as core binding factor (CBF) leukemia, and to a lesser extent in patients with normal cytogenetics [4]. However, intensified cytarabine consolidation has limited efficacy in patients with abnormal cytogenetics. These data are from a predominantly younger patient population, with only about 10% of the cohort older than 60 years. In yet an earlier study from CALGB, younger patients experienced a benefit from higher doses of cytarabine versus lower-dose infusional cytarabine [5]. Patients older than 60 received no apparent or uniform benefit from cytarabine intensification and

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Table 1
AML biology predict response and relapse after cytarabine + anthracycline chemotherapy.

Risk status	Cytogenetics	Molecular abnormalities
Better risk	inv(16) or t(16;16) or t(8;21) without *c-KIT* mutation, t(15;17)	Normal karyotype with ***NPM-1* mutation** in the absence of *FLT-3* ITD or Isolated biallelic *CEBPα*
Intermediate risk	Normal karyotype Trisomy 8 alone t(9;11) Other not defined	t(8;21), inv(16), t(16;16) with ***c-KIT* mutation**
Poor risk	Complex (≥3 clonal abnl) -5/5q-, -7/7q- Other 11q23 t(6;9), t(9;22) Monosomal karyotype Inv(3), t(3;3)	Normal karyotype with ***FLT-3 ITD*** mutation **TP53 mutation** **ASXL1 mutation**

Adapted from: NCCN Guidelines. Acute Myeloid Leukemia v2.2014, & ELN 2017

experienced significantly more neurotoxicity with high-dose cytarabine. Older patients are most likely to have abnormal or unfavorable cytogenetics and the least likely to benefit from intensified cytarabine consolidation, which poses a significant treatment dilemma in remission.

2. Cytogenetics and post remission therapy in older adults

AML is at the same time generally a disease of older people. The median age of individuals with newly diagnosed AML ranges from 68 to 72 years. AML incidence increases with age, peaking in the 80- to 84-year-old group. Data from the Swedish Acute Leukemia Registry, which contained 2866 cases of AML diagnosed from January 1997 through September 2005, found the median age to be 72 years (range, 16–97 years) with a mean of 68 years. Males were a median 71 years and females, 72 years [6].

By modeling the frequency of remission induction therapy over these data, it's clear that in patients older than 65, there's a rapidly diminishing number who undergo intensive therapy (Fig. 1). And most patients over 70 years do not receive intensive

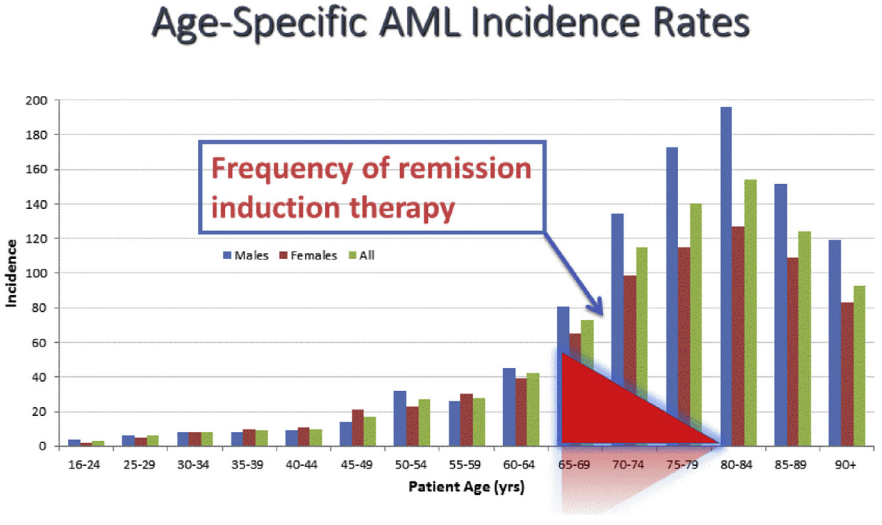

Fig. 1. A diminishing number of patients older than 65 years undergo intensive therapy, and most over 70 years do not receive intensive induction therapy. Cytogenetics could potentially be of use in this population to predict relapse or to model the best post remission therapy to administer.

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