Best Practice & Research Clinical Haematology 27 (2014) 241–246

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

6

Are adjuncts to induction chemotherapy worthwhile in the treatment of acute myeloid leukemia?

Farhad Ravandi, MD, Professor of Medicine *

Department of Leukemia, Unit 428, University of Texas – MD Anderson Cancer Center, USA

Keywords:
acute myeloid leukemia
adjunct
AML
anthracycline
chemotherapy
consolidation
cytarabine
induction
non-transplant
targeted agents

Research in non-transplant therapy of patients with acute myeloid leukemia (AML) has been focused on approaches to improve the efficacy of the backbone of cytarabine and anthracycline induction and consolidation regimens through modifications of dose and schedule of these agents and the addition of other cytotoxic agents. More recent advances in understanding the molecular biology of the disease have not only led to better prediction of responsiveness to these traditional regimens, but have also led to the identification of molecular targets for development of novel agents. Future research is likely to focus on determining which candidates are the best among such novel agents and what is the most appropriate way of incorporating them into the existing chemotherapy regimens. Identification of potent targeted agents may even have the potential of replacing cytotoxic therapy at least in some subsets of AML.

Progress in the treatment of patients with AML

Despite the gradual progress in the treatment of patients with acute myeloid leukemia (AML) in the last several decades, the significant improvements in survival are limited to specific subgroups of patients with the disease [1]. In general, younger patients have witnessed a more significant improvement in their survival and among them, patients with acute promyelocytic leukemia (APL), those with the core binding factor (CBF) leukemias, as well as a proportion of patients with normal karyotype (NK) AML have gained most from the advances in therapy [1]. Although many of these

* 1515 Holcombe Boulevard, Houston, TX 77030, USA. Tel.: +1 713 745 0394; Fax: +1 713 563 5774.
E-mail address: fravandi@mdanderson.org.

http://dx.doi.org/10.1016/j.beha.2014.10.005
1521-6926/

advances have been attributed to improvements in the supportive care strategies, numerous randomized and non-randomized clinical trials have explored whether variations in the dose of the established agents can benefit patients [2–6].

Is dose intensification at induction beneficial for subsets of patients with AML?

In a randomized study conducted by the Eastern Cooperative Oncology Group (ECOG), it was proven that in patients younger than 60 years, increasing the dose of daunorubicin from 45 mg/m^2 daily for 3 days to 90 mg/m^2 daily for 3 days led to an improvement in overall survival [2]. However, a more careful analysis of the subgroups treated demonstrated that this benefit was limited to the patients with biologically less adverse disease and not those with adverse cytogenetics, *FLT3*-ITD mutations, or older than the age 50 years [2]. Similarly, in a randomized trial conducted by the Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON), German AML Study Group (AMLSG), and Swiss Group for Clinical Cancer Research (SAKK), although an escalated dose of daunorubicin did not benefit patients over the age of 60 years overall, a clear survival advantage was reported for the younger subgroup within the study, patients aged 60–65 years, presumably due to their better disease and patient characteristics [3].

Other strategies of dose intensification have demonstrated a clear benefit only for the younger patients with more favorable leukemia biology. For example, the Medical Research Council (MRC) demonstrated that, overall, although the intensive fludarabine, cytarabine, granulocyte colony-stimulating factor (GCSF), and idarubicin (FLAG-Ida) regimen may not be superior to the less intensive regimen of daunorubicin and cytarabine (DA), among the younger patients who were able to tolerate two induction courses of FLAG-Ida, the relapse-free survival was clearly better. If they could deliver these two FLAG-Ida courses followed by high-dose cytarabine consolidation, the overall survival was a remarkable 95% and 63% for patients with favorable and intermediate-risk disease, respectively [5]. Similarly, the European Organization for Research and Treatment of Cancer (EORTC) and Gruppo Italiano Malattie Ematologiche dell' Adulto (GIMEMA) reported that using high-dose cytarabine in induction could significantly improve the overall survival for patients younger than 45 years but not those aged 46–60 years [6].

Therefore, it appears that we can simplistically divide patients with AML into those whose leukemic cells are sensitive to the effects of traditional cytotoxic agents and are able to withstand the toxicity of these agents and those who have leukemic cells that are inherently resistant to traditional cytotoxic agents (Table 1). Clearly dose intensification can potentially benefit the former but not the latter patients, for whom novel agents based on the biological features of the leukemic cells are needed.

Is there a role for a third cytotoxic agent in the induction regimens?

Several studies have also examined the benefit of the addition of a third cytotoxic agent to the combination of cytarabine and an anthracycline. In an early report, the Australian Leukemia Study Group demonstrated that the addition of etoposide to induction and consolidation therapy in patients

Table 1
Simplified classification of AML.

Classification of AML	Characteristics	Approach
Sensitive to conventional chemotherapy	• CBF leukemias (without *c-KIT* mutation) • Diploid AML with *NPM1* and *CEBPα* mutation (without *FLT3* mutation) • Others (younger patients without AHD)	Dose intensification may be helpful
Chemo-resistant	• AML with adverse cytogenetics • AML with *FLT3*-ITD • Others (older patients, younger patients with t-AML and/or AHD)	New agents needed

AHD, antecedent hematologic disorder; AML, acute myeloid leukemia; CEBPα, CCAAT enhancer binding protein alpha; CBF, core binding factor; FLT3, FMS-like tyrosine kinase-3; ITD, internal tandem duplication; NPM1, nucleophosmin1.