Progress in Acute Myeloid Leukemia

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Abstract

Significant progress has been made in the treatment of acute myeloid leukemia (AML). Steady gains in clinical research and a renaissance of genomics in leukemia have led to improved outcomes. The recognition of tremendous heterogeneity in AML has allowed individualized treatments of specific disease entities within the context of patient age, cytogenetics, and mutational analysis. The following is a comprehensive review of the current state of AML therapy and a roadmap of our approach to these distinct disease entities.

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Introduction

Acute myeloid leukemia (AML) is diagnosed at a rate of 18,000 new cases per year and accounts for > 10,000 deaths annually in the United States. Many AML experts and reviews emphasize a perceived lack of progress in the standard treatment of AML, commonly referred to as "7+3" (7 days of standard-dose cytarabine (araC); 3 days of anthracycline) and call for more research and newer therapies. Although more innovation and research are needed, important progress in diagnosis, treatment, and specialized care of AML has occurred which has not been publicized or broadly adopted.

In this review, we present a roadmap of AML treatment—one in which we: (1) recognize the tremendous disease heterogeneity; (2) individualize treatment; (3) move away from 7+3 to favor regimens with higher dose araC and nucleoside analogue doublets; (4) use targeted therapies when appropriate; and (5) cultivate a robust research program to understand the AML biology and offer investigational therapies to patients with the poorest prognoses. Recognizing the diverse approaches to AML treatment seen between specialized academic centers and community practices, and even among specialized centers, our programs are implemented through research-based clinical trials with the goal of high accrual, rapid knowledge acquisition and adoption, and maximal dissemination of positive therapeutic discoveries.

Acute myeloid leukemia is heterogeneous and requires accurate diagnosis and consideration of pretreatment disease and patient characteristics before instituting definitive treatment. A discussion of AML treatment should begin with a discussion of the various prognostic subtypes, which are closely linked to the chromosomal karyotype present in the leukemia cells.[1-3] The leukemia karyotype allows the segregation of patients with AML into 3 broad categories of favorable, adverse, and the ill-defined intermediate prognosis. Recent discoveries of recurrent somatic mutations in AML have allowed further refinement in prognostication and, in some cases, have provided opportunities for targeted treatment. We will discuss the treatment of AML as several distinct subtypes, starting with treatment options for entities that have established, highly curative therapies, moving on to refinements of current therapies for younger and older patients, and concluding with a look at newer targets and therapies on the horizon.

Treatment of Favorable Karyotype AML

Favorable karyotypes include t(8;21), inv(16), and t(15;17), the defining abnormality of acute promyelocytic leukemia (APL), which is discussed separately. The inv(16) chromosomal abnormality, and the t(16;16), lead to the formation of the CBFB/MYH11 (Core-binding factor, beta/Myosin heavy chain 11) fusion gene. This, along with t(8;21) (which leads to the formation of RUNX1 [Runt-related transcription factor 1]/RUNX1T1 fusion gene), represent the core binding factor (CBF) leukemias. The CBF AML subtypes have high response rates to induction and consolidation chemotherapy, and the potential for excellent long-term outcome. Steady progress has been made in this subgroup, improving overall survival (OS) rates from 55% in earlier studies to current rates of 75% to 80%.[3-8] The Cancer and Leukemia Group B studies demonstrated the benefit of adding 3 to 4 cycles of high-dose araC (HiDAC) consolidation after 7+3 induction in reducing the risk of relapse, improving disease-free survival (DFS), and improving OS rates to

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50% to 60%.[6,7] Bradstock et al investigated HiDAC-based induction followed by HiDAC consolidation versus standard-dose araC (SDAC) consolidation.[9] In the subset of favorable karyotype AML, they observed improved rates of relapse-free survival (RFS) and OS of 76% and 88%, respectively, when using HiDAC consolidation.[9] More recent studies involving fludarabine and HiDAC (FLAG) have reported complete response rates of 94% and improved RFS.[10] The combination of gemtuzumab ozogamicin (GO) or idarubicin (Ida) with FLAG further improved the cure fraction.[5,8] In the Medical Research Council (MRC) AML 15 trial, Burnett and colleagues randomized 1113 patients younger than 60 years to 1 of 3 induction regimens with or without GO,[8] and reported a significant OS benefit with the addition of GO in a predetermined subset of patients with favorable karyotype. In a recent multivariate analysis, the use of GO was found to be the most significant factor associated with improved OS.[11] Similarly, a Southwest Oncology Group (SWOG) trial[12] randomizing 595 patients to daunorubicin and araC with or without GO found, within the subgroup of favorable karyotype AML, a significant benefit in RFS and trend toward benefit in OS for patients who received GO (Table 1).[5,8,10,12,20] A meta-analysis of 5 trials combining chemotherapy with GO in AML induction concluded that the addition of GO led to a significant benefit in OS that outweighs any increase in early mortality, particularly in patients with favorable and intermediate-risk karyotype.[13] These and other studies provide justification to reinstate approval and marketing of this important agent.

Among this favorable subset, emerging data suggest that the presence of an associated *c-KIT* mutation or the presence of persistent minimal residual disease (MRD) after induction/consolidation might identify patients with a higher incidence of relapse and inferior outcome.[14-18] Dasatinib, a *KIT* inhibitor, has been studied in combination with chemotherapy in patients with c-*KIT*-mutated CBF AML, but the added benefit is not yet clear.[19] Standardization of the testing for mutations and MRD, and better *c-KIT* inhibitors are needed to address these high-risk cases. Since the removal of GO from the market, our approach to a patient with CBF AML is induction with FLAG-Ida[20] with age- and comorbidity-adjusted dosing, followed by 6 consolidation cycles. MRD is monitored routinely with quantitative real-time polymerase chain reaction (PCR) and acted upon in a risk-adjusted manner.

Treatment of APL

The treatment of APL is an important example of individualized treatment. The t(15;17) and variants lead to the promyelocytic leukemia-retinoic acid receptor alpha fusion gene and oncoprotein. The promyelocytic leukemia-retinoic acid receptor alpha protein acts as a dominant negative inhibitor of the wild type (WT) retinoic acid receptor, leads to differentiation block, and development of APL.[21] Discovery of the clinical activity of all-*trans* retinoic acid (ATRA) in APL, and understanding its mechanism in reversing the differentiation block, have revolutionized APL treatment.[21] Initial studies of ATRA and its combination with chemotherapy have transformed the disease from one that was highly fatal to one that is now highly curable.[22] Studies have also demonstrated the activity of single-agent arsenic trioxide (ATO) in APL by a slightly different mechanism, in patients with relapsed and previous untreated disease.[23-29] Based on the activity of each these agents and on preclinical evidence of synergy, combination strategies have been tested.[30] Shen et al randomized 61 patients with newly diagnosed APL to ATRA, ATO, or the combination, followed by consolidation chemotherapy including anthracycline and araC.[26] They demonstrated similar high complete remission (CR) rates (> 90%)

Table 1 Recent Studies in CBF AML

Reference	Regimen		n	Median Age, Years	CR/CRp, %	RFS and EFS	OS
Borthakur et al, 2008[10]	FLAG		22	39	94	3-Year RFS: 86% versus 57% for FLAG versus IA	3-Year OS: 80% versus 66% for FLAG versus IA
	FA		45	47			
	IA with or without G-CSF		47	36			
Borthakur et al, 2012[5]	FLAG-GO		50	48	96	85%	78%
Borthakur et al, 2013[20]	FLAG-Ida		38	51	98	No difference versus FLAG/GO	No difference versus FLAG/GO
Burnett et al, 2011[8]	ADE/DA 3+10/ FLAG-Ida	With GO	72	49	85[a]	NR	79% versus 51% in favor of combination with GO ($P = .001$)
		Without GO	65	49	87[a]		
Petersdorf et al, 2013[12]	Daunorubicin 45 mg/m^2 and araC	With GO	37	47	78	Significantly better with GO in CBF ($P = .043$)	Trend toward benefit for CBF leukemias in combination with GO ($P = .12$)
	Daunorubicin 60 mg/m^2 and araC	Without GO	44	48	93		

Abbreviations: ADE = cytarabine, daunorubicin, and etoposide; AML = acute myeloid leukemia; araC = cytarabine; CBF = core binding factor; CRp = complete remission with incomplete platelet recovery; DA 3+10 = 3 days of daunorubicin and 10 days of cytarabine; EFS = event-free survival; FA = fludarabine and high-dose cytarabine; FLAG = fludarabine, high-dose cytarabine, and granulocyte colony-stimulating factor (filgrastim); G-CSF = granulocyte colony-stimulating factor; GO = gemtuzumab ozogamicin; IA = idarubicin and high-dose cytarabine; Ida = idarubicin; OS = overall survival; RFS = relapse-free survival.

[a]Represents CR in all patients, whereas other values are CR only in the CBF subset.