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REVIEW

Emerging strategies for high-risk and relapsed/refractory acute myeloid leukemia: Novel agents and approaches currently in clinical trials

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ABSTRACT

High-risk acute myeloid leukemia (AML) is defined by clinical and biologic features that predict for poor response to induction chemotherapy and high risk of relapse. Despite even the most aggressive and well-developed strategies for care, most patients succumb to the disease. No currently available treatment has demonstrated consistent efficacy in terms of remission induction or long-term survival. This review will highlight some of the emerging strategies to treat high-risk AML with an emphasis on clinical trials of novel strategies currently enrolling patients. Targeted molecular therapies, novel cytotoxics, and immune-based therapies are under investigation for the management of high-risk AML. Some of the agents covered include tyrosine kinase inhibitors targeted to AML specific oncoproteins, nanoparticle formulations of existing drugs, nucleoside analogs, monoclonal antibodies, chimeric antigen receptors, bispecific T-cell engaging antibodies, and vaccines. As our understanding of the biology of AML has improved, targeted therapy for AML has emerged, offering to change not only response rate, but also the nature of response. Differentiation, rather than necrosis or apoptosis, is often seen in response to targeted agents and may be seen more frequently in the future. Interventions that might be more widely used in the near future include FLT3 inhibitors and nanoparticle formulations of drugs already known to have activity in the disease. Long term immune therapy holds significant promise.

1. Introduction

Clinically and biologically, acute myeloid leukemia (AML) in adults is a heterogeneous disease, characterized by unique risk profiles. High-risk AML clusters in older adults and is biologically and clinically characterized by a number of factors (Table 1). At diagnosis, if a patient has adverse molecular or cytogenetic features, an antecedent hematological disorder (typically myelodysplastic syndrome or myeloproliferative neoplasms), a prior cytotoxic chemotherapy (therapy-related AML), or an extramedullary disease (eg. CNS disease, myeloid sarcoma), they would conventionally be considered high-risk. Advancing age may not truly qualify as high-risk: while the biology in this group is usually more aggressive, high-risk could also include inability to tolerate standard therapy. The prognosis of most patients older than 70 years of age with AML is often poor (with the notable exception of acute promyelocytic leukemia) with intensive chemotherapy; among the elderly, not only is it common to see complex cytogenetics, but also it is common to see adverse cytogenetic and molecular features. The 8-week mortality exceeds 30% and the median survival is less than 6 months. As with any other malignancy, performance status and comorbid conditions have a significant impact on survival rates. Given that, physiological age is probably more important than chronological age. Moreover, certain patients initially considered favorable- or intermediate-risk might later declare themselves as high-risk if they have AML refractory to two cycles of induction therapy, a short duration of remission, or relapse following an allogeneic hematopoietic cell transplant (HCT) [1–7].

Despite decades of research and clinical trials, high-risk AML is still associated with a bleak long-term outcome. Unfortunately, there has been no regulatory pathway to approval of novel agents based on adverse disease biology or clinical features that predict for adverse outcome [8–10]. Clinical trials typically do not rigorously and prospectively risk-stratify patients with AML, although lately there has been an attempt to define more homogenous populations for the purpose of drug-approval. Conclusions about the response to therapy with regard to risk must then be made retrospectively, frequently in the setting of a variety of consolidation strategies. In the therapeutic management of high-risk AML, practitioners still have a very limited portfolio. For patients who can tolerate it, the only therapy that offers a chance at long-term disease-free survival is still standard induction with

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Table 1
Risk assessment for patients with AML.

Risk	Cytogenetic features	Molecular features	Clinical features
Favorable	t(8:21), inv(16) or t(16:16)	Mutated CEBPA or NPM1	N/A
Intermediate	Normal or trisomy 8	FLT3-ITD, mutation in KIT, TET2, MLL-PTD, DNMT3A, ASXL1, or PHF6	N/A
High-risk	-5/-7, 11q23, 20q-, 3 or more	N/A	Prior cytotoxic chemotherapy (therapy-related AML), extramedullary disease (eg. CNS, myeloid sarcoma), antecedent hematologic disorder (MDS, MPN), relapse after allogeneic HCT, or refractory to 2 cycles of 7 + 3 induction

cytarabine/anthracycline-based therapy (hereafter referred to as 7 + 3) and consolidation with high-dose cytarabine or allogeneic HCT. Allogeneic HCT has been the only strategy that seems to improve the otherwise dismal outcome after conventional induction and consolidation chemotherapy [5]. Unfortunately, those who might benefit most from an allogeneic HCT are also those most likely to be ineligible for transplant either due to failure of induction chemotherapy or early relapse [11]. Given that traditional therapies have proven largely ineffective for this group of patients, clinical trials constitute a preferred management pathway. This review will highlight some of the emerging strategies to treat high-risk AML.

2. Targeted molecular therapy with FLT3 inhibitors

Although there are many possible targets in AML, few have been exploited therapeutically in a clinically significant way. In about 20% of AML samples, internal tandem duplication (ITD) mutations in FLT3 are detected and are associated with inferior outcome [12]. An additional 5–10% of patients with AML harbor a tyrosine kinase domain (TKD) constitutively activating point mutation in FLT3, commonly at the activation loop residue D835, though this is less prognostic than the ITD form [13,14]. Given the success of kinase inhibitors in other diseases, FLT3 has been a target of choice for years, though early FLT3 inhibitors showed disappointing results. This was thought to be largely attributable to the lack of potency, selectivity, and favorable pharmacokinetic properties [15–17]. Newer agents may be more auspicious. For an overview, see Table 2.

3. Sorafenib

Off-label use of sorafenib may offer some benefit in relapsed/refractory FLT3-ITD AML. However, the use of sorafenib during induction and consolidation, especially for elderly patients with AML, has not been as encouraging, and even shows toxicity. In one trial, elderly patients (median age 68) received 7 + 3 and up to two cycles of intermediate-dose cytarabine consolidation [18]. 201 patients were randomized 1:1 to receive either sorafenib or placebo between the chemotherapy cycles and for up to 1 year after the beginning of therapy. Sorafenib not only failed to improve EFS or OS, regardless of the subgroup (including those with FLT3 ITD), but also caused a higher treatment-related mortality and lower CR rates. Due to higher toxicity, fewer patients received consolidation. In another study, a phase II trial was performed with 43 patients, 93% of whom had leukemia characterized by FLT3-ITD, median age of 64, and monthly cycles of 5-azacytidine given for 7 days with continuous sorafenib [19]. The response rate was 46%, including 10 (27%) complete response with incomplete count recovery (CRi), 6 (16%) complete responses (CR), and 1 (3%) partial response. The median duration of response was 2.3 months with a wide range: 1–14.3 months. The median number of cycles required to achieve CR/CRi was two. In another study in 13 younger patients (median age 47) with relapsed/refractory FLT3-ITD AML treated with sorafenib, 12 showed clearance or near clearance of bone marrow myeloblasts after 27 (range 21–84) days with evidence of leukemia differentiation [20]. The sorafenib response was lost in most patients after 72 (range 54–287) days but the FLT3 and downstream effectors remained suppressed. Resistant cells expressed several genes including ALDH1A1, JAK3, and MMP15, whose functions were unknown in AML and both ITD and TKD at D835 were identified in leukemia initiating cells (LICs) from samples prior to and after sorafenib treatment. This suggests that there may be preexisting LICs bearing both FLT3-ITD and TKD mutations that were selected out and expanded during treatment. In summary, sorafenib appears to provide a useful option for treatment of relapsed/refractory AML patients but has not yet been shown to be a good choice when incorporated into induction and consolidation in older patients. However, a large prospective study is needed to confirm the results from the small observational studies.

4. Quizartinib

Quizartinib (AC220) was arguably the first FLT3 inhibitor to achieve a meaningful single-agent activity with a composite complete remission (CR) rate of approximately 50% in a phase II study in patients with relapsed/refractory FLT3-ITD AML [21,22]. Interestingly, in 13 of 14 FLT3-ITD AML patients treated with quizartinib, terminal myeloid differentiation of BM blasts was observed in association with a clinical differentiation syndrome [23]. In vitro, primary blasts cocultured with human BM stroma, FLT3 inhibition with quizartinib induced cell-cycle arrest and differentiation rather than apoptosis [23]. In an as yet unreported multicenter, international phase 2 study (accrual completed and interim clinical results presented in abstract form) in adults with relapsed/refractory AML, quizartinib was administered as a single agent [23]. Final results remain to be seen, but an interesting laboratory

Table 2
Activity of FLT3 inhibitors in FLT3-ITD AML.

Agent	Single agent activity	Response duration	Resistance mechanism	Differentiation seen?
Sorafenib	ORR 92% (N = 12/13 with 6 CRi, 6 nCRi)	Median 72 days	Possibly expression of ALDH1A1, JAK3, and MMP15. TKD mutation at D835.	Yes
Quizartinib	CRc 48% (N = 92/191)	Median 79 and 89 days in two cohorts	Mutated C/EBPα or TKD mutation at F691 or D835	Yes, with differentiation-like syndrome
Midostaurin	2% PR (N = 1/35)	60 days	Unknown	Not reported
Ponatinib	30% ORR (N = 3/10)	3–6 months	Unknown, though the only responders with FLT3 inhibitor-naive	Not reported