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Reasons for optimism in the therapy of acute leukemia

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A B S T R A C T

Distinct progress has been made in recent years in the therapy of acute leukemia. For acute myeloid leukemia (AML), this progress has been anchored in the increased understanding of genomic complexity. Multiple targets and the relationships among them pose new challenges along with new possibilities for the development of targeted therapies. A number of new drugs are in early clinical development for AML, one of which centers on the role of isocitrate dehydrogenase (IDH) in malignancy. Epigenetic modulation, intracellular pathways, and the microenvironment are all being explored for possible therapies to treat AML. Dramatic clinical progress has also been made in therapy of acute lymphoblastic leukemia (ALL) with the rapid approval of blinatumomab, a bispecific T-cell engager antibody. Yet caution must also be exercised—not every mutation is an epigenetic target and early publication of clinical data is often misleading. Until the survival outcome for adult patients with acute leukemia improves, further inquiry into the biology of the disease and progress in the development of new therapies are needed.

Definite progress has been made in recent years in the therapy of acute myeloid leukemia (AML). This progress is anchored in an increasing understanding of genomic complexity. Along with this

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understanding come an ever-growing number of therapeutic targets that bring with them opportunities as well as major challenges in the development of targeted therapies. A recent paper by Estey et al. published in Blood highlights the major challenges to the development of targeted therapies in AML [1]. These include the limitations of preclinical studies, the inclusion of only one targeted agent in each trial, the delay in investigating new agents with chemotherapy, the difficulty selecting the optimal patient population, the question of whether eligible patients must have the target, and establishing the best endpoints for efficacy.

Despite these challenges, there has been real progress. Multiple new drugs for AML are currently in the early phase of clinical development (Table 1) [2]. One in particular is based on the known role of isocitrate dehydrogenase (IDH) in malignancy. IDH occurs in three isoforms, IDH1, IDH2, and IDH3. IDH1 is found in the cytoplasm and peroxisomes and IDH2 is located in the mitochondria. Both IDH1 and IDH2 catalyze the oxidative decarobxylation of isocitrate to alpha ketoglutarate using NADP as a cofactor to yield NADPH. Mutations in IDH1 and IDH2 confer neomorphic activity onto the mutant IDH enzyme; instead of catalyzing the conversion of isocitrate to alpha ketoglutatrate, the mutant proteins act to reduce alpha ketoglutarate to beta hydroxyglutarate, blocking normal cellular differentiation.

IDH1 mutations occur in about 7.0% of AML cases and IDH2 mutations occur in about 13% [3]. The agent AG-221, an inhibitor of IDH2, achieved a complete response of 33% and a partial response or stable disease in 60% in a phase 1 trial of 45 relapsed/refractory AML patients. Only 2 patients had progressive disease in this cohort [4]. This is unprecedented in AML, considering the nature of this relapsed/refractory population, and provides an incentive to further identify the driving mutations in AML and develop appropriate agents.

A word of caution is in order, however. Regarding genomics, it is important to keep in mind that not every mutation is a therapeutic target. Futhermore, for clinical efficacy, multiple targets may need to be targeted. In two recently published elegant studies, separate groups emphasize that clonal hematopoiesis with somatic mutations is common and occurs in approximately 10% of older adults, among whom only a very small number actually progress to myeloid neoplasms [5,6]. This situation suggests that hematologists perhaps should consider clonal hematopoiesis in AML to be of "undetermined significance," as it is in multiple myloma with monoclonal gammopathy of undetermined significance (MGUS|) [7].

Caution is also called for in the clinical field as a reminder that early publication of clinical data is often misleading. Several years ago anthracycline dose intensification was shown to be an important

Table 1
Multiple new drugs for AML in phase 1/2 [2].

Target type	Target	Agent
Epigenetic modulation		
	IDH1/IDH2	AG-221
	DOT1L	EPZ-5676
	DNMT3	Azacytidine
		Decitabine
Intracellular pathways		
	BCL-2	ABT-737
	PI3K/AKT/mTOR	BKM120
		Deferolimus
		Rapamycin
		OSI-027
		BEZ-235
	MEK/ERK4	AZD 6244
		Trametinib
		GSK 2141795
Microenvironment		
	CXCR4	Plerixafor
		MDX-1338
		BL-8040
	PIM-1,2,3	AZD 1208
	Axl	BGB 324