Best Practice & Research Clinical Haematology 26 (2013) 269–274

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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

6

# New agents: Great expectations not realized

Jeffrey E. Lancet, MD, Professor, Senior Member [a,b,*]

[a] Oncologic Sciences, University of South Florida, Tampa, USA
[b] Department of Malignant Hematology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA

*Keywords:*
acute myeloid leukemia, AML
CPX-351
FLAM
flavopiridol
FLT3 inhibitor
gemtuzumab
tipifarnib
lintuzumab
laromustine
lestaurtinib
midostaurin
AC220
clofarabine
quizartinib
sapacitabine

A number of new agents in acute myeloid leukemia (AML) have held much promise in recent years, but most have failed to change the therapeutic landscape. Indeed, with the exception of gemtuzumab ozogamicin (which was subsequently voluntarily withdrawn from the commercial market), no new agent has been approved for acute myeloid leukemia (AML) beyond the 7 + 3 regimen, which was has been in use for over 40 years. This review touches upon the potential reasons for these failures and explores the newer therapeutic approaches being pursued in AML.



## Introduction

Despite a long list of drugs that have been in development to treat acute myeloid leukemia (AML), only a handful are still candidates and in a more advanced phase of testing (Fig. 1). With the exception of gemtuzumab ozogamicin (currently withdrawn from the commercial market), not a single agent has yet been approved for AML in the last 40 years. In the case of gemtuzumab ozogamicin, new and more recent data reveal promising effects upon survival when combined with traditional cytotoxic chemotherapy drugs [1,2].

Progress in drug development for AML is occurring within the arenas of “targeted” therapy, whereby leukemia-specific and pathogenic molecular targets are being therapeutically exploited, and

* Department of Malignant Hematology, Moffitt Cancer Center, 12902 Magnolia Drive, Tampa, FL 33612, USA. Tel.: +1 813 745 6841; Fax: +1 813 745 3071.
*E-mail address:* Jeffrey.lancet@moffitt.org.

1521-6926/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.beha.2013.10.007

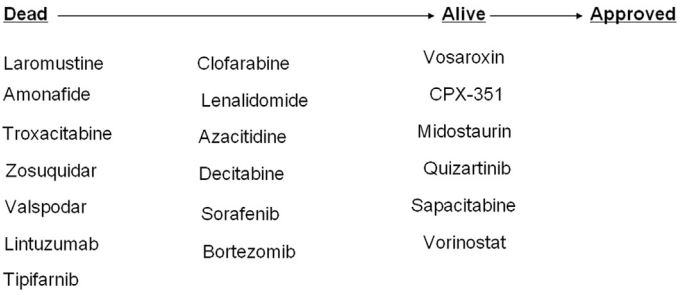


**Fig. 1.** Short list of new drugs in AML.

"non-targeted" therapy, where more potent DNA damaging agents and improved drug-delivery systems are being developed.

## Obstacles in drug development

A number of issues have hampered the development of effective new therapies in AML, including clinical trial design, choice of appropriate clinical endpoints in early phase development, and a lack of biomarker-driven trials.

The issue of optimal clinical trial design is a complex one, beyond the scope of this review. Nonetheless, certain aspects of clinical trial design with potentially negative impact upon drug development deserve mention. These include, first and foremost, small study size and lack of randomization in phase 2 testing, which create high likelihoods of either falsely positive results (which could lead to inappropriate phase 3 testing) or falsely negative results (which could lead to abandonment of an active compound) [3,4]. Examples of this would include empiric phase 2 testing of drugs such as clofarabine and laromustine in elderly AML patients, where it was determined that the drugs clearly had reasonable antileukemic activity, but the lack of a randomized setting created the impossibility of determining whether the research drug was superior to more traditionally used induction regimens in unselected patient populations [5,6]. In the case of laromustine, a negative phase 2 trial contributed to the eventual abandonment of this potentially useful agent for further development [5].

To this point also, clinical and molecular heterogeneity within the patient population of a trial that tests a novel or targeted agent could underestimate the true impact of the drug, if limited efficacy in restricted patient populations becomes diluted by a larger and more diverse patient population, often the case in larger randomized studies. Examples of more targeted agents failing to achieve desired endpoints in unselected, heterogeneous populations may be seen in the case of tipifarnib [7] and lintuzumab [8]. Tipifarnib is a farnesyltransferase inhibitor that originally showed promising activity in a large non-randomized phase 2 trial [9]. However, randomized testing in a large subsequent phase 3 trial failed to demonstrate a survival advantage compared to supportive care, suggesting that a targeted therapy with limited, albeit definite, activity could not be justified for generalized use in unselected patients [7]. Similarly, lintuzumab, a naked anti CD33 antibody, was tested against low-dose cytarabine in older patients who were not suitable for or who refused chemotherapy, demonstrating no survival advantage to adding lintuzumab [8]. Despite the clear ability of these agents to elicit antileukemic activity in selected patients in earlier studies, there was not enough benefit in a larger and more diverse patient population of patients to justify broader development. These problems can be potentially overcome by incorporation of molecular correlates into large empiric trials, or by retrospectively interrogating novel gene expression patterns, in order to better identify factors associated with response, such that future prospective trials are aimed at more specific patient populations likely to benefit [10,11].

Clinical endpoints in earlier phase studies themselves may be barriers to optimal drug development. For example, it is possible that response rate, often chosen as the primary endpoint in phase 2