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Will new agents impact survival in AML?

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ABSTRACT

In recent years, several drugs—including midostaurin, gilteritinib, and gemtuzumab ozogamicin, to name a few—have been approved or reapproved in the United States to treat patients with acute myeloid leukemia (AML). Yet survival rates for younger patients had improved with chemotherapy alone even before the approvals of these new agents. This begs the question whether the new therapies will actually have a positive impact on survival. The 5-year survival rate for older patients has also risen, again without the addition of these new agents. The challenge will be to incorporate new therapies and use them where they will have the greatest impact—major work for clinicians and researchers alike.

Introduction

The past few years have brought much activity in drug development for the treatment of patients with acute myeloid leukemia (AML), with the approval or reapproval in the United States of eight new drugs for various stages of disease, with some limitations by age (Table 1). Three additional drugs have received breakthrough designation from the US Food and Drug Administration (FDA) (Table 2).

The question is, what overall impact will these new agents have on AML? Will they markedly change the traditional survival curves, which now report a long-term survival rate between 40% and 45% in patients younger than 60 years [1–5]? Recent population data from the SEER (Surveillance, Epidemiology, and End Results) database indicate a 45% survival rate for patients younger than 65 with AML [6].

Survival

The survival of younger patients over the past 5 decades has dramatically improved, as demonstrated by the Eastern Cooperative Oncology Group (ECOG) survival data in patients younger than 60 (Fig. 1) [7]. The Medical Research Council (MRC) in Britain described similar data [4]. The importance here is that these advances have taken place without the addition of any new drugs for AML. Presumably, the increasing survival is related to advances in supportive care, better use of existing drugs, advances in

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Table 1
New agents for AML with recent regulatory approval.

Agent	Target	Advanced disease	Newly diagnosed	Age
Midostaurin	FLT3		+ +	
Gilteritinib	FLT3	+ +		
Gemtuzumab ozogamicin	CD33	+ +	+ +	
CPX-351	Cytotoxic		+ +	
Enasidenib	IDH2	+ +		
Ivosidenib	IDH1	+ +		
Venetoclax	BCL-2		+ +	≥75 years
Glasdegib	Hedgehog pathway inhibitor		+ +	≥75 years

Table 2
New agents with breakthrough designation.

Agent	Target	Advanced disease	Newly diagnosed	Age
GMI-1271	E-selectin	+ +		
Ivosidenib	IDH1		+ +	≥75 years
Quizartinib	FLT3	+ +		

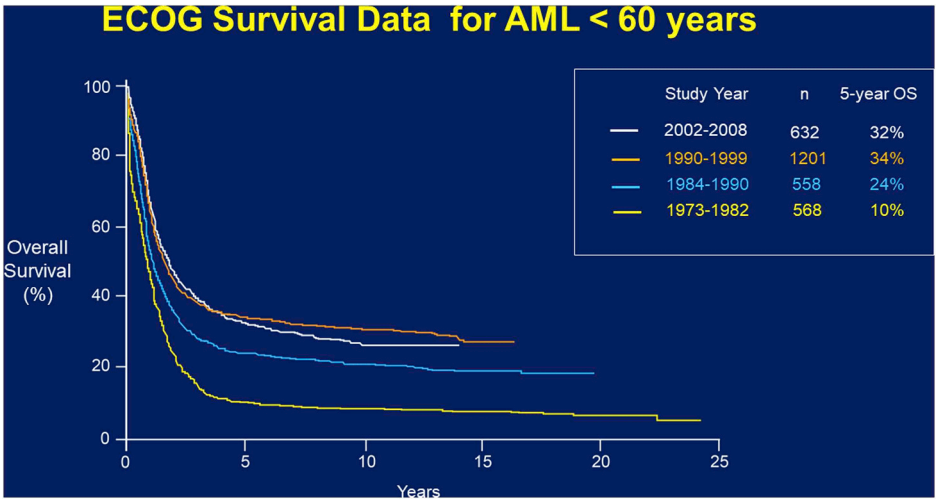

Fig. 1. ECOG survival data younger AML patients, 1973–2008.
Legend, Fig. 1. The graph shows improvements in survival rates over the decades for younger patients with AML, from 10% in the 1970s to 32% in 2002–2008. Updated from Tallman MS, Gilliland DG, Rowe JM. Blood 2005; 106:1154–1163.

transplantation, and a more refined understanding of the disease biology enabling more accurate prognostication. It can therefore be assumed that similar progress may be expected in the next decade, irrespective of any single new drug for AML. This has important considerations in predicting the impact of the new drugs recently made available for AML.

For many years, the survival data for older patients showed no improvement. Recently, however, some inroads have been made in treating the older adult population. Data from ECOG show that over the past decade, and probably for the first time, the 5-year survival rate for older patients has increased to between 15% and 20% (Fig. 2) [7].The follow-up is relatively long supporting these data. And again, this survival increase has occurred without any new drugs.

Exciting new drug combinations are now being explored for treating older patients. One example is venetoclax combined with hypomethylating agents, such as azacitidine or decitabine [8]. At a median of 8.9 months on study, 67% of patients achieved a complete response (CR) or CR with incomplete count recovery (CRi). Patients with poor-risk cytogenetics achieved a CR + CRi rate of 60%, and those 75 or older achieved a 65% CR + CRi. Similar data have been reported using the combination of venetoclax and low-dose cytarabine [9]. At the same time, prospective randomized studies are ongoing to assess the true magnitude of the addition of venetoclax. Furthermore, like all new drugs, the safety and toxicity has yet to be learned. A prolonged pancytopenia is not an infrequent occurrence with the venetoclax combinations. Longer follow-up is clearly needed for a more definitive assessment.

The standard 7 + 3 arm—daunorubicin plus cytarabine—of a recently completed North American Intergroup study (E2906) for older patients with follow-up of more than 4 years had notable results [10]. The patients achieved a CR rate of 45% and minimal residual disease (MRD) negativity of 40%. Patients who achieved both a CR and were MRD negative had an impressive median

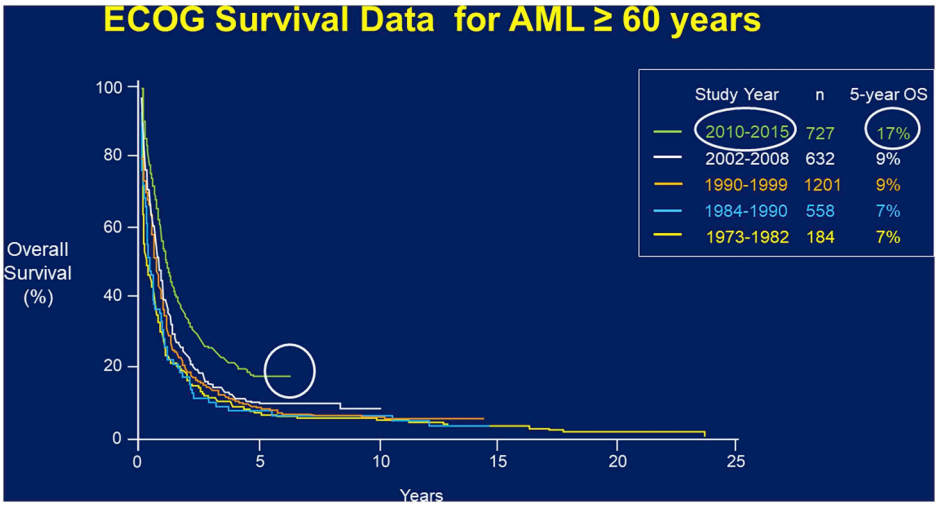

Fig. 2. ECOG survival data for older AML patients, 1973–2015.
Legend, Fig. 2. The graph shows improvements in survival rates over the decades for older patients with AML, from 7% in the 1970s to 17% in 2010–2015. Updated from Tallman MS, Gilliland DG, Rowe JM. Blood 2005; 106:1154–1163.

survival of 30.5 months. Clearly, 7 + 3 is still a valuable option for older adults. At the present time, intensive chemotherapy remains the only treatment that has demonstrated the ability to consistently achieve long-term disease-free survival [10].

Integrating new therapies

Looking again at advances that occurred over the past 5 decades (Fig. 3), the question arises as to where these agents will have the greatest impact. If one focuses, for example, on improving induction therapy, new targeted agents and chemotherapeutic drugs have been approved and may now be added to therapeutic regimens. Midostaurin should be incorporated into the therapy of any FLT3-positive patient, and CPX-351 for patients with secondary AML. It is quite likely that in the next few years more specific FLT3 inhibitors, such as gilteritinib, quizartinib, and crenolanib, will be incorporated into the induction phase of newly diagnosed patients with AML who are FLT3 positive.

Chemotherapy remains a relatively unpopular choice for augmentation of induction (Table 3). This is the case despite some very compelling phase 3 data. For example, only a limited number of individuals routinely use gemtuzumab ozogamicin in induction. Even fewer would use cladribine upfront despite excellent data. Perhaps even fewer would incorporate lomustine or clofarabine into induction, despite excellent phase 3 data for these agents [11–14]. We clearly have a long way to go in AML to further define and better describe appropriate places for the use of all these new drugs.

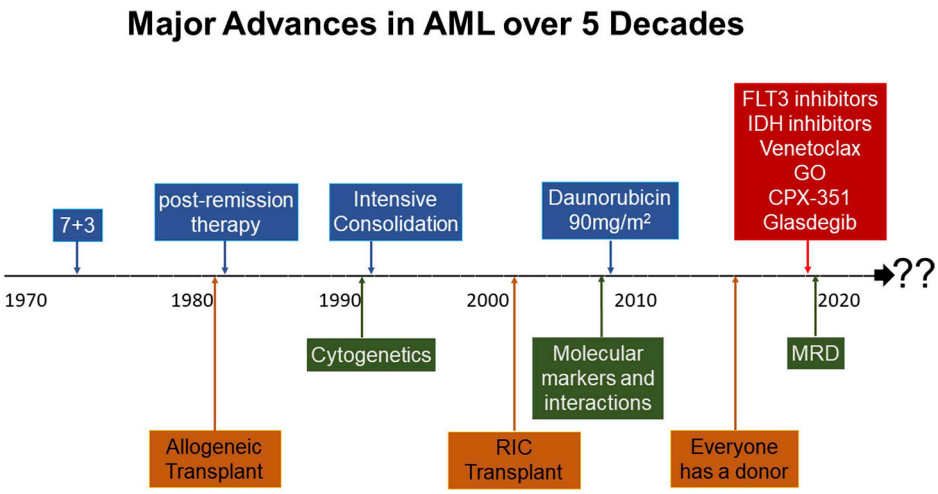

Fig. 3. Major advances in AML.
Legend, Fig. 3. This timeline shows major advances taking place in AML, including progress in the understanding of the biology of the disease, alterations in dosages of the standard therapy and the addition of new therapies, and developments in allogeneic stem cell transplant.

Table 3
Selective adoption of standard of care in AML.

Popular Choices for Induction Therapy	Unpopular Chemotherapy Choices for Augmentation of Induction Therapy
Midostaurin	Cladribine
CPX-351	Clofarabine
	Lomustine
	Gemtuzumab ozogamicin

Declaration of competing interest

Consulting fees: Biosight, Cellect.

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