

Will new drugs cure acute myeloid leukaemia?

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Summary

There are many new therapies approved to treat acute myeloid leukaemia (AML) including conventional and targeted drugs, and immune therapy. Most improve diverse outcomes including event- and relapse-free survivals and survival. However, most effect sizes are small and failure rates by 2 years are high. Based on the data reviewed above I conclude: (1) many new AML therapies target specific AML sub-types; (2) none are proved better than intensive radiochemotherapy in persons who could receive either therapy; (3) there is disagreement defining who can or cannot receive intensive therapy;

(4) there are important problems with several new drug approvals; (5) azacitidine and venetoclax may be the new *standard-of-care* in elderly persons with AML judged unable to receive intensive therapy; and (6) new drugs are welcome but have not had a big impact on long-term survival of most people with AML.

Keywords

Acute myeloid leukemia, targeted therapy, efficiency.

Introduction

There are many new therapies approved to treat acute myeloid leukaemia (AML) including new conventional and targeted drugs and immune therapy. A summary of new AML drugs is displayed in Figure 1 increasing from one approval every 6 years to one approval every 150 days, a 12-fold increase.

The question I consider is whether these new therapies will cure AML. My discussion is divided into 3 categories: (1) conventional drugs; (2) targeted therapies; and (3) immune therapy.

New drugs

I consider 4 new drugs: (a) venetoclax [1]; (b) CPX-351 [2]; (c) CC-486 [3]; and (d) glasdegib (\pm low-dose cytarabine) [1-4]. Results of these, quite recent trials demonstrate that, although each new drug, alone or combined with previously-approved drugs improved outcomes, there remains a high rate of failures by 2 years.

Targeted drugs

Four targeted drugs are approved in AML including: (1) midostaurin; (2) gilteritinib; (3) enasidenib, and (4) ivosidenib. Results of recent trials of these 3 drugs are published, and the survival curves can be compared [5-8]. Except for enasidenib, these drugs improve outcomes but 2-year failure rates are high. A US trial *Beat AML* in persons with newly-diagnosed AML assigned subjects with druggable mutations to targeted or conventional drugs. There was no important difference in outcomes [9]. Therefore, according to recent estimates, current targeted drugs are likely to help only a limited subgroup (ca. 10 percent) of patients with acute myeloid leukemia [10].

Immune therapy

Gemtuzumab, an anti-CD33 monoclonal toxin-linked antibody, is the only approved immune therapy of AML [11]. It modestly improves outcomes and is rarely used.

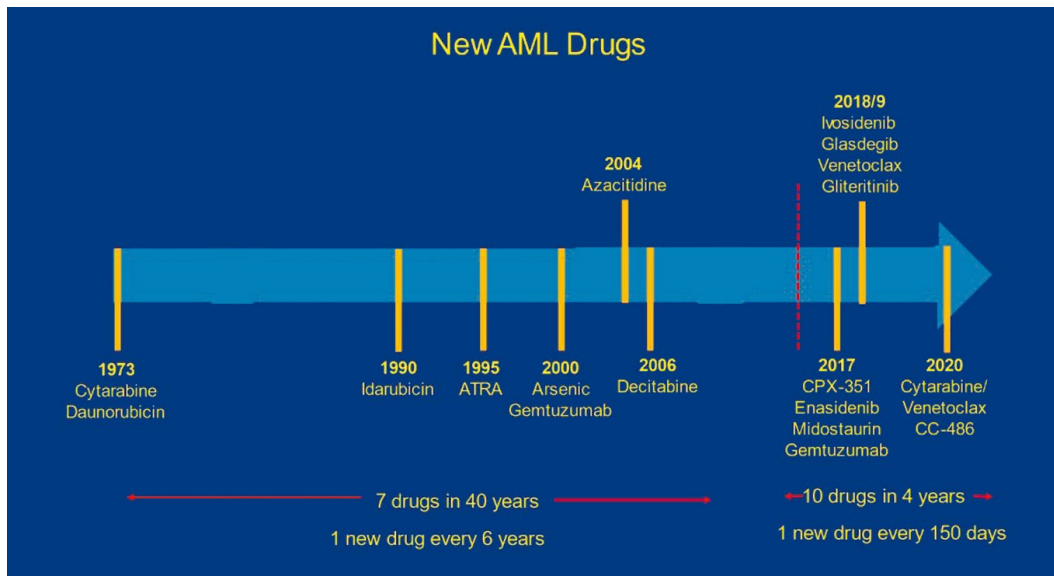


Figure 1. Drug approvals in AML 1973–2020

Issues in new drug approvals

Several important issues confound analyses of the appropriate use of new drugs in AML including: (1) who is *unfit* for intensive therapy? (2) no randomized trial proves less-intensive therapy is better than conventional intensive therapy amongst persons who could receive either; (3) what is the best endpoint for new drug approvals; (4) what is the appropriate comparator for a new drug approval; (5) several recent approvals are for unstudied populations; (6) recent approvals will decrease enrollment in clinical trials; and (7) most new drugs improve survival only slightly and long-term results remain unsatisfactory [12]. Table 1 displays data indicating not everyone benefits from a new drug such as venetoclax [1].

Table 1. Differential effects of azacitidine and venetoclax in sub-cohorts

Who benefits from azacitidine + venetoclax		
	Benefit	No benefit
Sex	Female	Male
Age	≥75 y	<75 y
Country	US/EU	Russia/China/Japan
ECOG PS	1	≥2
Cytogenetics	Intermediate	Poor
Mutations	IDH1/IDH2	FLT3/TP53/NPM1
MDS changes	No	Yes
Bone marrow blasts	≥30%	<30%

Table 2 shows although azacitidine and venetoclax improve survival of older persons with AML there remains a major loss of potential life-expectancy. Finally, Table 3 displays the cost of several new AML drugs compared with conventional drugs.

Table 2. Impact of azacitidine and venetoclax on reversing loss in life-expectancy

Remaining life-expectancy				
Age	Expected age	Added years	Venetoclax azacitidine	Lost years
Male 75	86	11	2 years	9
Female 75	89	14	2 years	12

Table 3. Relative per year costs of some new drugs

Cost per Cycle or 1-Year (USD)	
Cytarabine/Daunorubicin	\$1,500
Azacitidine	\$4,400
Gilteritinib	\$105,000
Enasidenib	\$120,000

Conclusions

Based on the data I review above I conclude: (1) many new AML therapies target specific AML sub-types; (2) none are proved better than intensive radiochemotherapy in persons who could receive either therapy; (3) there is disagreement defining who can or cannot receive intensive therapy; (4) there are important problems with several new drug approvals; (5) azacitidine and venetoclax may be the new *standard-of-care* in elderly persons with AML judged unable to receive intensive therapy; and (6) new drugs are welcome but have not had a big impact on long-term survival of most people with AML.

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Conflict of interest

RPG is a consultant to: BeiGene Ltd., Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Pharmaceuticals Inc. and CStone Pharmaceuticals. Medical Director of FFF Enterprises Inc, on the Board of Directors: RakFond Foundation for Cancer Research Support. Scientific Advisory Board: Antegene Biotech LLC, StemRad Ltd. *Author Contribution:* I conceived, wrote and submitted the typescript for publication. *Ethics Approval:* None required.

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Будут ли новые лекарства излечивать острый миелоидный лейкоз?

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Резюме

Существует много новых методов лечения, одобренных для лечения острого миелоидного лейкоза (ОМЛ), включая традиционные и таргетные препараты, а также иммунотерапию. Большинство из них улучшают различные исходы, включая бессобытийную и безрецидивную выживаемость. Однако в большинстве случаев выраженность эффекта невелика, и высока частота неуспешной терапии при 2-летнем наблюдении. Основываясь на данных, рассмотренных выше, сделаны выводы о том, что: (1) многие новые методы лечения ОМЛ направлены на терапию определенных подтипов ОМЛ; (2) ни один из них не оказался лучше, чем интенсивная химиолучевая терапия пациентов, которые могли бы получать любой из этих видов лечения;

(3) существуют разногласия по поводу того, кто может или не может получать интенсивную терапию; (4) существуют серьезные проблемы с одобрением нескольких новых лекарственных препаратов; (5) азациитидин и венетоклакс могут быть новым стандартом лечения пожилых людей с ОМЛ, признанных неспособными получать интенсивную терапию; и (6) новые препараты должны рассматриваться, но пока не оказали большого влияния на долгосрочное выживание большинства пациентов с ОМЛ.

Ключевые слова

Острый миелоидный лейкоз, таргетная терапия, эффективность.