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Publication Date

2020-09-01

DOI

10.1016/j.leukres.2020.106420

Leukemia Research 96 (2020) 106420

Contents lists available at ScienceDirect

Leukemia Research

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

Research paper

Analysis of estimated clinical benefit of newly approved drugs for US patients with acute myeloid leukemia

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ARTICLE INFO

Keywords:
Acute myeloid leukemia
Drug costs
Chemotherapy

ABSTRACT

The increased number of available United States Food and Drug Administration (FDA)-approved drugs indicated for acute myeloid leukemia (AML) have generated considerable interest and may have the potential to influence practice. We performed a retrospective cross-sectional study performed from September to November 2019 to determine 1) demographic and subgroup characteristics of patients with newly diagnosed cases of acute myeloid leukemia, 2) FDA data on drugs indicated for AML approved from 1969 through November 2019, 3) measures of response from drug labels, and 4) published reports documenting the response for drugs approved before the 1979 Labeling Act. We used publicly available data from the Food and Drug Administration (FDA), the American Cancer Society, the Leukemia and Lymphoma Society, and the U.S. Census Bureau. According to our estimation methods, cytarabine infused continuously for 7 days, with three short boluses of anthracycline over Days 1–3, the standard of care known as "7 + 3", continues to have the largest population benefit. The maximum cost per course of treatment for an average regimen is enasidenib for salvage therapy, estimated to be around $120,131. The minimum cost was $1,662.50 for standard 7 + 3 chemotherapy. The mean and median cost for all AML treatments was $43,784.26 and $35,083.70, respectively. While it is true that the number of available therapies approved by the FDA has increased dramatically, it is not yet clear how large of a clinical benefit we can expect to see from these new lines of therapies.

1. Introduction

Acute myeloid leukemia (AML) is the most common hematologic malignancy for adults[1], with median age of onset at 68 years. The treatment for AML stratifies itself based on those who can tolerate standard cytarabine and daunorubicin, or "7 + 3″ chemotherapy, and those who cannot, typically patients who are older or with significant comorbidities. Those who cannot tolerate the standard regimen, often due to age, poor European Cooperative Oncology Group (ECOG) Performance Status, or comorbidities such as congestive heart failure, chronic kidney disease, history of stroke/cerebrovascular disease, and peripheral vascular disease, are typically recommended to undergo less intensive treatments that include lower doses of cytarabine (LoDAC) or hypomethylating agents azacitidine or decitabine [2]. While cure rates and 5-year survival curves have improved for patients under the age of 60, prognosis for patients over 60 and/or with comorbidities is grim [3].

The lack of robust drugs beyond the standard of care for AML has led to the effort to identify new therapies and has yielded many U.S. Food and Drug Administration (FDA) approvals for genome-based drugs. While it is certainly true that the therapies approved by the FDA for treating AML have diversified, we wondered how much overall clinical benefit we can expect these new drugs to provide, given other factors such as cost and strength of evidence through cumulative response rate. We sought to provide an analysis of how much clinical benefit, defined by percentage of patients eligible and responsive to such therapy, that we can expect from these drugs recently indicated for AML therapy. Our analysis of AML therapies is similar to prior analyses in our research group estimating the eligibility and response of fibroblast growth factor (FGF) receptor drugs, checkpoint inhibitors and genome-driven cancer therapies in US patients with cancer, respectively [4–6].

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https://doi.org/10.1016/j.leukres.2020.106420
Received 20 May 2020; Received in revised form 8 July 2020; Accepted 9 July 2020
Available online 13 July 2020

2. Methods

2.1. Estimation of eligible patients and percentage of AML subtypes

Similar to prior work [4–6], we conducted a cross-sectional analysis to estimate the percentage of US patients with newly diagnosed cases of AML in 2019 who are (1) eligible for and (2) may respond favorably to drugs indicated by the FDA for AML. We estimated the annual incidence of AML by referencing all new AML diagnoses in 2019 [1]. We used this number as a proxy for the number of new AML cases per year, and therefore the number of AML patients eligible for therapy in 2019.

We sought to estimate the percentage of patients who cannot tolerate standard 7 + 3 chemotherapy and identified literature that suggests 7 + 3 is not recommended for patients older than 80 years old [7]. To estimate the percentage of U.S. citizens newly diagnosed with AML in 2019 who were aged 80 years or older, we identified the number of U.S. citizens who are 80 years and older by accessing U.S. Census Bureau 1-Year population estimates [8]. By multiplying the census data with age-specific incidence rates from 2011 to 2015 [9,10] which we used as a proxy for age-specific incidence [9,11], we calculated the estimated percentage of patients who cannot tolerate the standard of care.

Notably, some of the drugs are indicated for particular clinical subgroups of AML, as classified by the World Health Organization (WHO). We sought to estimate the percentage of AML patients in each relevant subgroup. We first referenced the WHO classification system, updated in 2016 [12] and then identified the literature to obtain the best estimates for the percentage of AML patients that comprise that subgroup.

Notably, many recently approved AML drugs are indicated for "genome-targeted" molecular signatures, including *FLT3* mutations, *IDH1/2* mutations, and CD33-expressing leukemic cells, which are important molecular subgroups in AML but not distinctly recognized by the WHO-based classification. We identified the most common genetic mutations in AML and estimated their prevalence in new AML cases in 2019 in the United States by extracting estimations from the literature [3,12–21]. For each genetic mutation indication, we referenced at least two publications to corroborate estimation of prevalence. If the prevalence of certain mutations fell within a percentage range, we reported the median value of the percentage in our calculations (e.g. a mutation found in 10 − 20% cases would be reported as 15 %).

2.2. Identification of AML drugs and estimation of clinical benefit

Between June 1969 and November 2019, we identified 12 drugs comprising 15 regimens indicated and approved for the treatment of acute myeloid leukemia. We excluded all-trans-retinoic acid (ATRA), a differentiation agent indicated for the AML subtype acute promyelocytic leukemia, from our analysis, since the addition of ATRA to cytarabine and daunorubicin ("7 + 3") has been well characterized as the standard of care for this particular subtype [22].

For drugs approved earlier than 1979, before the Content and Format for Labeling for Human Prescription Drugs Rule, or the 1979 Labeling Rule, specifically cytarabine (1969) and daunorubicin (1979), we obtained best overall response rates (ORR) from landmark clinical trials that led to approval and widespread use in practice [23]. For all other drugs, we accessed FDA labels from the Drugs@FDA.gov website for ten anti-cancer drugs that were indicated for the treatment of AML: decitabine (2006), azacitidine (2004), gemtuzumab ozogamicin (2017), CPX-351 (2017), venetoclax (2016), glasdegib (2018), midostaurin (2017), gilteritinib (2018), ivosidenib (2018), and enasidenib (2017) [24]. Indications (Section 2), the recommended dosage and schedule (Section 6), and clinical trial data that formed the basis for approval (Section 14) were extracted from the labels. Manuscripts reporting on the studies cited in the FDA label and announcement were also collected.

We defined "persons eligible for therapy" as the estimated number of new cases of AML in 2019 who fit the indication for each drug (e.g. if 10 % of all AML cases have an *IDH1* mutation, among all new cases, 2145 people could be eligible for therapy). Where possible, we extracted the best hazard ratio for comparison between control and experimental arm for each drug regimen. Since not all clinical trials employed methodologies that generated hazard ratios, we defined clinical benefit based on the best available overall response rate from trials that formed the basis of approval (FDA drug label). We used the overall response rate in the experimental group if the drug was compared with placebo control, a different drug regimen control, or if assessed in single-arm trial. We pre-defined the overall response rate (ORR) as the sum of the complete remission (CR) and partial remission or complete remission with incomplete hematologic recovery (CRi) rate. We noted if there were discrepancies in CR or CRi criteria among key trials. We then multiplied the best ORR by the estimated persons eligible for therapy to assess the potential benefit each regimen could bring the population.

2.3. Analysis of inflation-adjusted cost of AML drugs

An analysis estimating cost of each anti-cancer drug regimen indicated for an average U.S. patient with AML, per average course of therapy and capped at one year of treatment, was performed. An average U.S. patient was defined as a patient with the U.S. mean for body mass index (BMI) and therefore mean body surface area, which is important for calculating intravenous anticancer treatments. Average wholesale price (AWP) for each FDA-approved drug regimen was extracted at time of analysis using data available from Red Book: Pharmacy's Fundamental Reference 2019. We looked at median duration of treatment to understand the length of potential expenses. If median duration of treatment was not given, we used median progression-free survival as a surrogate, and if median progression-free survival was not given, we used total induction duration as proxy. If none of these variables were reported, we calculated 1 year of therapy for each drug regimen.

2.4. Statistical analysis

Calculations and data visualization were performed using R statistical software, version 3.5.0. This study was not submitted for institutional review board approval as it did not involve personally identifiable data, and all data are publicly available. The study was conducted between October 2019 and December 2019.

3. Results

3.1. Estimation of percentage of patients fit for 7 + 3 standard chemotherapy

There were an estimated 21,450 new cases of AML in 2019 [1]. This number is increased by 9% from 2018, which had an estimated 19,520 new cases of AML (American Cancer Society Facts and Figures 2018). We estimate that 84.1 % of new cases are ineligible for 7 + 3 and 15.9 % are ineligible. [7,11].

3.2. Estimation of the percent of patients eligible for particular drugs

Of all new AML cases, about 33 % [3,17,18] are estimated to have aberrant *FLT3* genes. Of this *FLT3*-mutant subgroup, 75 % will have *FLT* internal tandem repeats (25 % of all new cases) and 25 % will have point mutations (8% of all new cases). About 7–14 % of all new AML cases are estimated to have *IDH1*, while 8–19 % are estimated to have *IDH2* mutations, and about 85–90 % of patients will have CD33+ leukemic cells expressed [14,15]. The full estimation of percentage of patients falling under certain categories in AML are summarized in Table 1.

Table 1
Characteristics of drug regimens approved by the U.S. Food and Drug Administration for acute myeloid leukemia, 1969 through 2019. APML was excluded as it has a distinct mechanism and has been validated as the standard of care for this particular subtype of AML.

Regimen Number	Drug Regimen	Date Approved	Indication	Category	Basis of Approval	Key clinical trial forming basis of FDA approval	Indication	Percent of New Cases Eligible for Regimen	Source	Number of New Cases Eligible for Regimen in 2019	Best Overall Response Rate (CR + CRh) on studies forming basis of FDA approval	Hazard Ratio	Duration Type/ Median Duration of Treatment
1	7 + 3 (cytarabine + daunorubicin)	1969 June 17 and 1979 December 19	newly diagnosed	cytotoxic	N/A	https://drive.google.com/file/d/1eOJdxEy6JjIo3fx6JWIoA_a11gGECXmt/view?usp = sharing [23]	indicated for remission induction of acute non-lymphocytic leukemia of adult and pediatric patients; blast phase of CML; acute lymphocytic leukemia, meningeal leukemia	0.841	Shallis et al. 2019 [11], SEER 2019 data [10], Walter 2015 [7], Kumar 2010 [13]	18,039	0.75	N/A	induction
2	azacitidine	2004 May 19	newly diagnosed precluding	hypomethylating	ORR (CR + PR)	DOI: 10.1200/JCO.2002.04.117 [27]	older patients (> 80 assumption) with AML; indicated for treatment of patients with the following FAB myelodysplastic syndrome (MDS) subtypes: Refractory anemia (RA) or refractory anemia with ringed sideroblasts (RARS) (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL). (1) AND 30 % blasts	0.159	Shallis et al. 2019 [11], SEER 2019 data [10], Walter 2015 [7], Kumar 2010 [13]	3411	0.23	N/A	6 cycles
3	decitabine			hypomethylating		DOI: 10.1002/cncr.21792 [28]		0.159		3411	0.17	N/A	4 cycles

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Table 1 (*continued*)

Regimen Number	Drug Regimen	Date Approved	Indication	Category	Basis of Approval	Key clinical trial forming basis of FDA approval	Indication	Percent of New Cases Eligible for Regimen	Source	Number of New Cases Eligible for Regimen in 2019	Best Overall Response Rate (CR + CRh) on studies forming basis of FDA approval	Hazard Ratio	Duration Type/ Median Duration of Treatment
		2006 May 2	newly diagnosed precluding		ORR (CR + PR)		older patients (> 80 assumption) with AML; indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups		Shallis et al. 2019 [11], SEER 2019 data [10], Walter 2015 [7], Kumar 2010 [13]				
4	GO	2017 September 1	newly diagnosed, relapsed/ refractory	flow-cytometry detected	ORR (CR + PR)	DOI: 10.1200/JCO.2015.64.0060 https://doi.org/10.1634/theoncologist.2017−0604 [29]	treatment of relapsed or refractory CD33 + AMl in adults and pediatric patients 2 years and older; treatment of newly diagnosed CD33 AML in adults	0.875	De Propis et al. 2011 [14], Ehninger et al. 2014 [15]	18,769	0.33	0.69	3 doses
5	7 + 3 GO	2017 September 1	newly diagnosed,	flow-cytometry detected	EFS	https://doi.org/10.1016/S0140−6736(12)60485−1 [30]	treatment of relapsed or refractory CD33 +	0.875	De Propis et al. 2011 [14],	18,769	0.27	0.81	not reported

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Table 1 (*continued*)

Regimen Number	Drug Regimen	Date Approved	Indication	Category	Basis of Approval	Key clinical trial forming basis of FDA approval	Indication	Percent of New Cases Eligible for Regimen	Source	Number of New Cases Eligible for Regimen in 2019	Best Overall Response Rate (CR + CRh) on studies forming basis of FDA approval	Hazard Ratio	Duration Type/ Median Duration of Treatment
			relapsed/ refractory				AMl in adults and pediatric patients 2 years and older; treatment of newly diagnosed CD33 AML in adults		Ehninger et al. 2014 [15]				
6	CPX-351	2017 August 3	newly diagnosed	cytotoxic	OS	doi: 10.1200/JCO.2017.77.6112. [31]	treatment of adults with newly-diagnosed therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	10 − 20%; 24 − 35%	SEER 2019 data [10], Arber et al. 2016 [12] Grandfeldt Ostgard et al. 2015 [16]	5363	0.477	0.69	62 days
7	azacitidine venetoclax	2018 November 21	newly diagnosed precluding	genome-targeted	CRR, DoR	doi.org/10.1016/S1470 − 2045(18)30,010-X [32]	newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy, chronic lymphocytic leukemia/small lymphocytic lymphoma	0.159	Shallis 2019 [11], SEER 2019 data [10], Walter 2015 [7]	3411	0.59	N/A	4 cycles
8	decitabine venetoclax	2018 November 21	newly diagnosed precluding	genome-targeted	CRR, DoR	doi.org/10.1016/S1470 − 2045(18)30,010-X [32]	newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy, chronic lymphocytic leukemia/small lymphocytic lymphoma	0.159	Shallis 2019 [11], SEER 2019 data [10], Walter 2015 [7]	3411	0.61	N/A	4 cycles

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Table 1 (*continued*)

Regimen Number	Drug Regimen	Date Approved	Indication	Category	Basis of Approval	Key clinical trial forming basis of FDA approval	Indication	Percent of New Cases Eligible for Regimen	Source	Number of New Cases Eligible for Regimen in 2019	Best Overall Response Rate (CR + CRh) on studies forming basis of FDA approval	Hazard Ratio	Duration Type/ Median Duration of Treatment
9	LoDAC venetoclax	2018 November 21	newly diagnosed precluding	genome-targeted	CRR, DoR	DOI: 10.1200/JCO.18.01600 [33]	newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy, chronic lymphocytic leukemia/small lymphocytic lymphoma	0.159	Shallis 2019 [11], SEER 2019 data [10], Walter 2015 [7]	3411	0.54	N/A	4.2 months
10	LoDaC glasdegib	2018 November 21	newly diagnosed precluding	genome-targeted	OS	doi: 10.1038/s41375−018-0312−9 [34]	≥75 years old OR who have comorbidities that preclude use of intensive induction chemotherapy.	0.159	Shallis 2019 [11], SEER 2019 data [10], Walter 2015 [7]	3411	0.17	0.46	2.7 months
11	7 + 3 midostaurin	2017 April 28	newly diagnosed	genome-targeted	OS	https://dx.doi.org/10.1056 %2FNEJMoa1614359 [35]	FLT3-mut AML, newly diagnosed, systematic mastocytosis	0.33	Dohner et al. 2014 [3], Daver et al. 2019 [17], Marcucci et al. 2011 [18]	7079	0.59	0.77	induction
12	gilteritinib	2018 November 28	relapsed/ refractory	genome-targeted	OS	DOI: 10.1056/NEJMoa1902688 [36]	indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.	0.33	Dohner et al. 2014 [3], Daver et al. 2019 [17], Marcucci et al. 2011 [18]	7079	0.21	0.64	5 cycles
13	ivosidenib	2019 May 2	newly diagnosed precluding	genome-targeted	CRR, DoR	doi: 10.1182/blood.2019002140. [37]	IDH1-mut AML newly diagnosed	0.10	Dohner et al. 2014 [3], Marcucci et al. 2010 [19], Patel	2145	0.424	N/A	4.3 months

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Table 1 (*continued*)

Regimen Number	Drug Regimen	Date Approved	Indication	Category	Basis of Approval	Key clinical trial forming basis of FDA approval	Indication	Percent of New Cases Eligible for Regimen	Source	Number of New Cases Eligible for Regimen in 2019	Best Overall Response Rate (CR + CRh) on studies forming basis of FDA approval	Hazard Ratio	Duration Type/ Median Duration of Treatment
									et al. 2011 [20]				
14	ivosidenib	2018 July 20	relapsed/ refractory	genome-targeted	CRR, DoR	10.1056/NEJMoa1716984 [38]	IDH1-AML, refractory and relapsed	0.10	Dohner et al. 2014 [3], Marcucci et al. 2010, Patel et al. 2011 [20]	2145	0.429	N/A	3.5 months
15	enasidenib	2017 August 1	relapsed/ refractory	genome-targeted	CRR, DoR	doi: 10.1182/blood-2017 − 04-779405. [39]	treatment for IDH2-AML, refractory and relapsed	0.15	Dohner et al. 2014[3], Marcucci et al. 2010 [19], Green et al. 2011 (21), Patel et al. 2011 [20]	3218	0.23	N/A	5 cycles

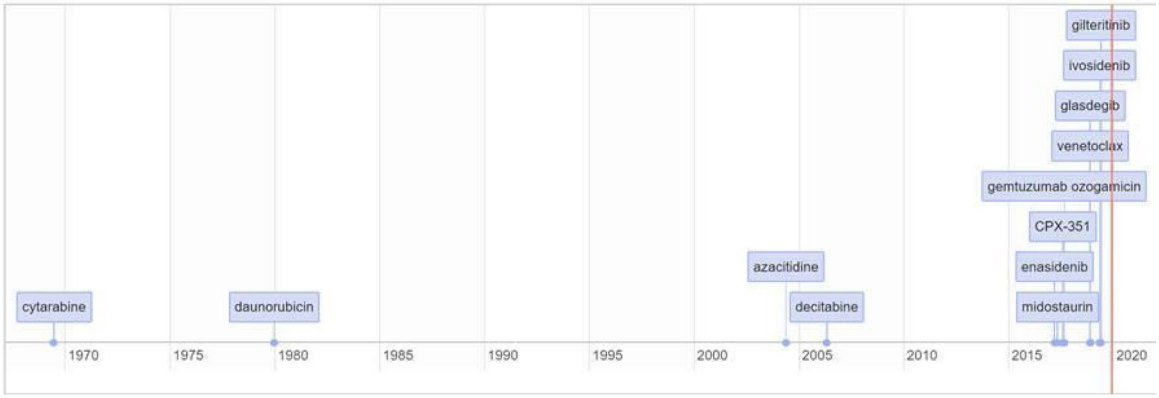

Fig. 1. Timeline of drugs approved by the U.S. Food and Drug Administration for treatment of acute myeloid leukemia.

3.3. Characteristics of AML drug regimens, and analysis of the evidence that led to basis of FDA approval

Between 1969 and 2019, 12 drugs comprising 15 regimens were approved for the treatment of newly diagnosed or relapsed or refractory (R/R) AML. The median year of approval was 2008. Of all drugs, 83 % (10/12) were approved between 2004 and 2019, and 66 % (8/12) have been approved since 2017 (see Fig. 1). Collectively, in addition to AML, these drugs were also approved for the following indications: myelodysplastic syndromes in the French-American-British system, systemic mastocytosis, chronic lymphocytic leukemia /small lymphocytic leukemia.

Among the 15 distinct drug regimens, 3 (20 %) are indicated for newly diagnosed cases of AML fit for intensive chemotherapy: 7 + 3, CPX-351, and midostaurin in combination with 7 + 3. Six out of 15 (40 %) are indicated only for newly diagnosed cases unsuitable for intensive chemotherapy: azacitidine, decitabine, venetoclax in combination with either azacitidine, decitabine, or low-dose cytarabine, and glasdegib in combination with low-dose cytarabine. Two of 15 drug regimens (13.3 %) are indicated for relapsed/refractory cases only: enasidenib and gilteritinib. Single agent gemtuzumab ozogamicin (GO), 7 + 3 GO, and ivosidenib are 3 regimens of 15 (20 %) indicated for both newly diagnosed and relapsed/refractory AML cases.

More than half of the drug regimens (9/15, 60 %) are indicated for patients with specific genetic mutations that can be detected with whole genome sequencing, and are “genome-targeted”. Single-agent GO and 7 + 3 GO are 2 of 15 regimens (13.3 %) with a specific indication that can be detected by flow cytometry (e.g. sorting for CD33+ cells). Regular approval was given to of 12/15 (80 %) regimens, while accelerated approval was given to just 3 of 15 regimens.

In trials that formed the basis of approval for enasidenib, ivosidenib, and venetoclax with low-dose cytarabine (3 of 15, 20 %) single-arm studies were employed. In their clinical trials, decitabine, azacitidine, and single-agent gemtuzumab ozogamicin were tested against best supportive care only. Venetoclax was tested in combination with azacitidine or with decitabine, and glasdegib was tested in combination with low-dose cytarabine against low-dose cytarabine only.

Of all 15 drug regimens, CPX-351 (a liposomal formulation of 7 + 3) was the only single agent tested against the 7 + 3 standard treatment. Midostaurin has been tested in combination with the standard of care, 7 + 3, against standard treatment only. Gemtuzumab ozogamicin was tested in combination with 7 + 3 against 7 + 3 only. Randomized trials against 7 + 3 were conducted for 3 out of 15 (20 %) of drugs for AML: single-agent gemtuzumab ozogamicin, CPX-351, and 7 + 3 midostaurin. Of these, only 7 + 3 midostaurin had a randomized, double-blind, placebo-controlled study.

Of the drug regimens approved for AML, about 26.7 % (4/15) were approved on the basis of overall survival, defined as the time from randomization to time of death from any cause. The remaining (11/15, 73.3 %) were approved on the basis of overall response rate (the sum of CR and CRi rates, typically) or complete response rate and median duration of response. The overall response rate of any AML drug regimen did not match or surpass that of the combination of cytarabine and daunorubicin (75 %). Full analysis and summary of clinical trials, including best rates, are collected in Table 1.

To generate an estimation of the potential population benefit, we multiplied the best ORR (FDA drug label) by percent of patients eligible to receive each regimen. By our method, 7 + 3 has the largest population benefit. These findings are summarized in Fig. 2.

3.4. Estimated inflation-adjusted cost analysis for 1 year of therapy demonstrated cytotoxic treatments are on average, more affordable

An analysis estimating cost per average course of therapy, capped at one year of treatment, for the average U.S. patient was performed. Wholesale price cost by AML drug for an average regimen for an average U.S. patient is summarized in Fig. 3. The maximum cost for an average regimen is enasidenib for salvage therapy, estimated to be around $120,131. The minimum cost was $1,662.50 for standard 7 + 3 chemotherapy. The mean and median cost for all AML treatments was $43,784.26 and $35,083.70, respectively. Salvage therapies were more expensive than first line therapies.

4. Discussion

Acute myeloid leukemia, with its complex genomic landscape, remains a challenging disease to manage. In the decades since establishing itself as the standard of care, a total of 197 trials, among those 98 randomized phase III trials, for leukemia and myeloma have helped establish the correct, dose, schedule, and sequence of 7 + 3 therapy [25]. We find that in terms of patient eligibility, cumulative response rate, and cost per average regimen, 7 + 3 remains dominant over newer agents. Our empirical analysis reaches a similar conclusion as expert reviews on the impact of novel anti-cancer therapies in this setting [26].

One potential benefit of genome-targeted drugs is their improved toxicity profile compared to cytotoxic drugs. Yet, potential adverse effects are still inherent in all drugs and must not be understated. Gemtuzumab ozogamicin, which was initially approved in 2000 for AML, was voluntarily withdrawn from the market due to safety and efficacy concerns; it was later approved in 2017 at a different dose and schedule. Adverse effects such as differentiation syndrome may occur in 10 % and up to 20 % of patients who take enasidenib or ivosidenib, and 3% of those who take gilteritinib [24]. Hyperbilirubinemia was observed in 81 % of patients in enasidenib.

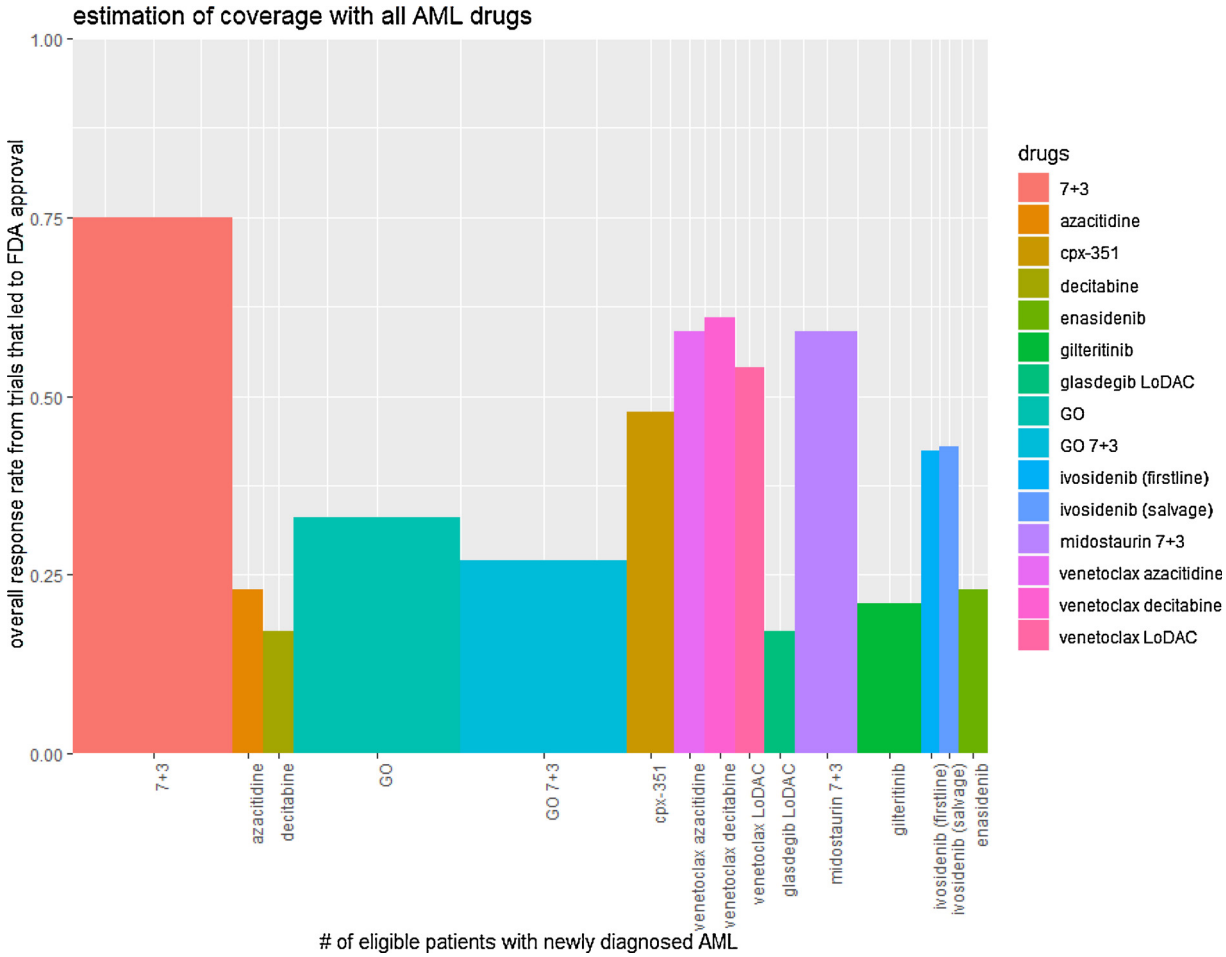

Fig. 2. Estimated number of patients eligible for each drug approved for AML (width) plotted against estimated clinical benefit based on best overall response rate (height) in trials that formed the basis for FDA approval. 7 + 3, standard cytarabine 100 mg/km^2, and daunorubicin 44 mg/km^2;GO, gemtuzumab ozogamicin; LoDAC, low-dose cytarabine. Width is relative and does not sum to 100 % because of overlapping usages.

5. Strengths and limitations

There are 3 strengths and 3 limitations to this study. The strengths of this study include our novel approach. Ours is the first research group to attempt to estimate the percentage of AML patients belonging to each subgroup, which will help patients understand the magnitude of potential benefit of a single regimen on the entire AML population. Secondly, our approach attempts to systematically assess the clinical benefit of drugs, in the context of all clinical trials that formed the basis of approval. Lastly, our figures aim to succinctly communicate the clinical benefit patients and providers might expect with different AML regimens.

In terms of limitations we acknowledge that the estimation of eligibility based off AML subcategories is challenging, as AML is a genetically heterogeneous disease. For example, *FLT3*, *IDH1*, and *IDH2*mutations, which are detected by genetic analysis, and CD33 expression, which is detected by flow cytometry, may not be and is likely not mutually exclusive. This limitation may inflate our estimate of impact. For eligibility estimates based off the literature, we sought to find multiple sources that demonstrated a consistent picture. Lastly, our estimate for patients who cannot tolerate standard 7 + 3 chemotherapy was based off empirical epidemiologic analyses. While we believe our methodology is robust, we encourage others to conduct similar analyses.

Second, we did not consider off-label use of these drugs. As such, we may underestimate the number of patients whose have been on these drugs. It would be difficult to ascertain benefit from off-label use, by virtue that such regimens have not been formally evaluated by the FDA.

Lastly, with our average wholesale price analysis, we estimated the upper bound of cost for an average patient but acknowledge there may be a wide range of pricing of these drugs, especially due to variation in healthcare coverage. We also assume universal access to these medications. Since the cost of drugs is an unfortunate barrier to maximizing clinical benefit, we believe providing an upper level estimate is appropriate.

6. Conclusions

In summary, the estimated percentage of patients who are eligible for and who respond to AML drugs are reasonable but remain modest compared to the standard of care. These agents often have costs far greater than 7 + 3. As costs for salvage therapies intended for relapsed and refractory patients remain high, the cost effectiveness remains uncertain. We believe our study provides an opportunity to compare the population-level effect and the expected cost of each FDA-approved AML regimen based off of empirical epidemiological estimates. In doing so, we promote the maxim that we must keep the two factors patients care about most – how well a regimen works and how much it costs – at the center of discussion.

We hope these findings may help policy makers, biomedical companies, media outlets, and physicians have more accurate and realistic discussions about the current clinical benefit that these AML drugs may provide. Furthermore, we hope these results will motivate researchers to develop drugs that benefit an even larger percentage of individuals

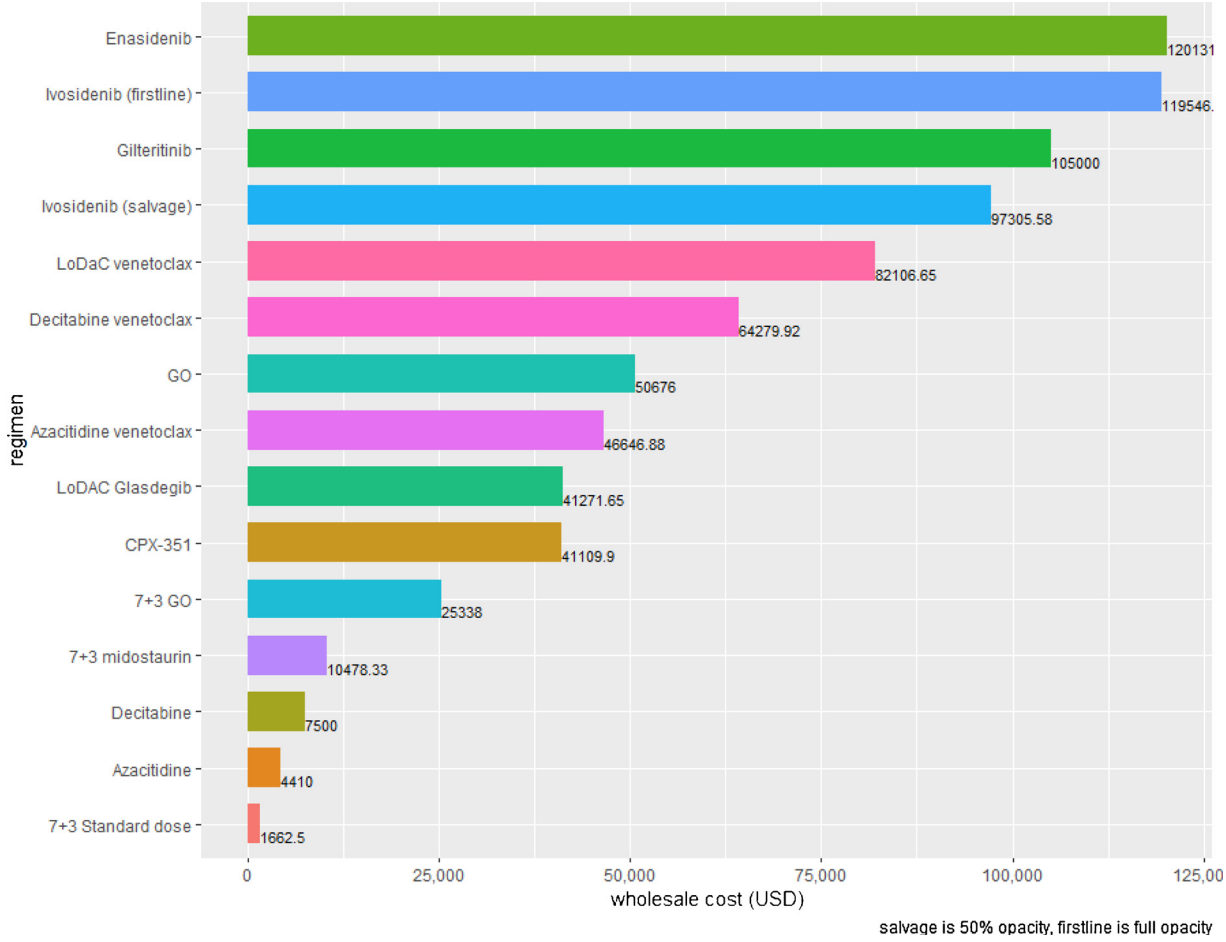

Fig. 3. Cost analysis for average length course, capped at one year of treatment, assuming average U.S. patient body mass index (BMI) and corresponding body surface area (BSA) for each FDA-approved drug regimen.

with cancer than these current estimates.

Disclosures

V.P. reports (Research funding) Arnold Ventures (Royalties) Johns Hopkins Press, Medscape (Honoraria) Grand Rounds/lectures from universities, medical centers, non profits, and professional societies. (Consulting) UnitedHealthcare. (Speaking fees) Evicore. (Other) Plenary Session podcast has Patreon backers. A.A.T. and M.M. have nothing to report.

Funding

This work was supported by the John and Laura Arnold Foundation.

Acknowledgements

We gratefully acknowledge access to drug pricing databases that allowed for this analysis. Feedback from colleagues Quiana Klossner, Jennifer Gill, and Diana Herrera-Perez was also greatly appreciated.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2020.106420.

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