Current Hematologic Malignancy Reports (2019) 14:171–178
https://doi.org/10.1007/s11899-019-00510-2

HEALTH ECONOMICS (N KHERA, SECTION EDITOR)

Trends in Clinical Benefits and Costs of Novel Therapeutics in AML: at What Price Does Progress Come?

Jennifer E. Vaughn[1] · Veena Shankaran[2,3,4,5,6] · Roland B. Walter[2,7,8,9]

Published online: 11 May 2019

Abstract

Purpose of Review Since 2017, eight novel agents have been approved for the treatment of acute myeloid leukemia (AML) in the USA. Here, we review the clinical benefits and costs associated with these drugs.

Recent Findings For some of the newly-approved drugs, clinical benefit has been documented in randomized trials. Others received accelerated approval based on surrogate endpoints in early phase trials. All, however, carry significant costs and toxicities. Cost-effectiveness analyses are so far only available for midostaurin, CPX-351, and gemtuzumab ozogamicin.

Summary Recently approved drugs for AML have varying levels of evidence for clinical effectiveness and because of associated high costs may further increase the overall economic burden of AML care. This issue is complex and whether novel AML drugs will cost-effective will depend on multiple factors, including their ability to improve survival and quality of life while simultaneously reducing the costs of healthcare resource utilization.

Keywords Acute myeloid leukemia · Novel therapeutics · Clinical benefit · Cost-benefit · Health economics

Introduction

Acute myeloid leukemia (AML) is a hematologic malignancy characterized by clonal, abnormally differentiated cells of the hematopoietic system accumulating in the bone marrow, blood, and possibly other organs [1]. Without treatment, survival is measured in days to weeks [2]. Fit people with AML are usually offered induction chemotherapy, which results in the achievement of complete remission (CR) in the majority of cases. Still, despite post-remission chemotherapy and/or allogeneic hematopoietic cell transplantation (HCT), relapses are common and only a minority of the affected individuals will be long-term survivors [3, 4]. Outcomes are distinctly worse in patients who are not considered candidates for intensive therapeutic strategies [5, 6]; with the aging population, this subset of patients is ever expanding. Thus, there is an ongoing need for more effective AML therapies.

This article is part of the Topical Collection on *Health Economics*

✉ Jennifer E. Vaughn
jvaughn@vtc.vt.edu

Veena Shankaran
vshank@uw.edu

Roland B. Walter
rwalter@fredhutch.org

[1] Department of Medicine, Virginia Tech Carilion School of Medicine, 2 Riverside Dr., Roanoke, VA 24016, USA

[2] Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[3] Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA

[4] Division of Medical Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

[5] Department of Pharmacy, University of Washington School of Medicine, Seattle, WA, USA

[6] Department of Pharmacy, Seattle Cancer Care Alliance, Seattle, WA, USA

[7] Division of Hematology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA

[8] Department of Epidemiology, University of Washington School of Public Health, Seattle, WA, USA

[9] Department of Pathology, University of Washington School of Medicine, Seattle, WA, USA

After the combination of 7 days of infusional cytarabine and 3 days of an anthracycline ("7 + 3") became the standard of care induction chemotherapy (IC) regimen almost five decades ago [7], progress in AML therapy has been primarily limited to advances in supportive care. However, a flurry of new drugs has become available over the last 2 years, an evolution partly due to the increasing understanding of the genetic and molecular abnormalities underlying AML pathogenesis, as well as innovation in drug delivery methods. Given the poor outcomes with currently available treatments, especially for medically less-fit patients and those with cytogenetically/molecularly defined high-risk disease features, several of these drugs have gained expedited approval by the US Food and Drug Administration (FDA) based on data from single-arm, uncontrolled phase 1/2 trials conducted in highly selected patients. Until results from better controlled (ideally, randomized) trials become available, the clinical benefits of the latter category of drugs are difficult to appraise.

As the number of available new drugs increases, it is also anticipated that the cost of AML care will escalate. Newly approved drugs for hematologic malignancies currently cost between $30,000 and $200,000 per year [8, 9]. This is in addition to an already expensive "standard" treatment characterized by conventional chemotherapeutics, complex supportive care, extended hospitalizations, and, for some, allogeneic HCT [10]. From a societal standpoint, attention and planning regarding the economic impact of AML care are therefore imperative. However, the impact of new drug costs may not be so straightforward. While it would seem obvious that expensive pharmaceuticals would inevitably drive costs upward, in actuality, a few unknowns exist. First, will these drugs provide "value" to the healthcare system and patients, a model which has traditionally taken into account the cost of achieving not only increased quantity but also quality of additional life? Second, will drugs that are more effective at getting patients into CR lead to a reduction in the costs accrued from transfusion support, hospitalizations, antibiotic use, and even the need for allo HCT? And third, as many of the new drugs are given orally or with simplified administration schedules, will the reduced need for inpatient administration abate the cost associated with the drugs themselves?

The following article will review what is currently known about the clinical benefits and associated costs of eight AML drugs recently approved by the FDA: midostaurin, gilteritinib, enasidenib, ivosidenib, venetoclax, glasdegib, CPX-351, and gemtuzumab ozogamicin (GO). In addition, we will discuss the complexities of judging the costs of these drugs relative to their projected benefits—both clinical and in terms of their potential to reduce other expenditures within the healthcare system.

Clinical Benefits of "Targeted" Agents for AML

The increasing understanding of the molecular landscape of AML has led to the identification of disease-relevant pathways that lend themselves as therapeutic targets in AML [1]. In some cases, drugs that intervene in these aberrant signaling pathways have indeed resulted in incremental improvements in CR rates and survival. One example of such a "targeted" agent is midostaurin, a multi-kinase inhibitor with activity against the receptor tyrosine kinase FLT3. Mutations in the *FLT3* gene occur in 30% of AML cases, are more prevalent in the elderly, and have—at least in the form of internal tandem duplications—traditionally inferred worse prognosis [4]. CALGB10603 ("RATIFY") was a global, randomized, placebo-controlled phase 3 trial that demonstrated a significant overall survival advantage in newly diagnosed *FLT3*-mutated AML patients treated with midostaurin in addition to IC (74.7 months vs. 25.6 months in patients given IC + placebo [$p = 0.009$]). Event-free survival was also significantly prolonged with the addition of midostaurin (8.2 months vs. 3.0 months for placebo [$p = 0.002$]) [11••]. This trial led to the approval of midostaurin in combination with frontline IC in *FLT3*-mutated AML in 2017. More recently, another tyrosine kinase inhibitor, gilteritinib (ASP2215), was approved based on interim results from the ADMIRAL trial, a phase 3, randomized controlled trial evaluating the efficacy of gilteritinib versus salvage chemotherapy for relapsed/refractory FLT3-mutated AML. Twenty-one percent of patients included in this study achieved a CR or CR with incomplete hematologic recovery (CRi), and 31.1% of transfusion-dependent patients achieved durable transfusion independence [12].

Mutations in the isocitrate dehydrogenase 1 and 2 (*IDH1*, *IDH2*) genes are present in 8% and 12% of AML cases, respectively [13]. Two orally available, potent, reversible, and selective inhibitors specific for mutated forms of IDH, enasidenib (targets mutant IDH2) and ivosidenib (targets mutant IDH1), have been approved for the treatment of relapsed/refractory *IDH*-mutated AML. Enasidenib received accelerated FDA approval in 2017 after a phase 1 dose-escalation study with expansion cohorts demonstrated a 40.3% response rate among *IDH2*-mutated relapsed/refractory AML, with remissions lasting a median of 5.8 months [14•]. The IDH1 inhibitor, ivosidenib, was approved in mid-2018 after a phase 1 dose-escalation/cohort expansion study demonstrated a CR + CR with partial hematologic improvement (CRh) rate of 30.4% among patients with *IDH1*-mutated relapsed/refractory disease [15•]. Of additional importance, transfusion independence was achieved in 34% and 35% of transfusion-dependent patients treated with enasidenib and ivosidenib, respectively [14•, 15•].

Efforts to improve outcomes in patients considered ill-suited for intensive AML therapies are ongoing. Venetoclax, a small molecule inhibitor of the BCL2 protein, has been

approved for the treatment of elderly/frail AML patients in combination with low-dose cytarabine or an azanucleoside (azacytidine or decitabine). These approvals were based on single-arm, uncontrolled phase 1/2 studies demonstrating responses of some durability in over 60% of HCT-ineligible patients [16•, 17•]. In treatment-naïve AML patients > 65 years of age, an overall survival of > 17.5 months was reported with the combination of venetoclax and either azacytidine or decitabine [17•]. Glasdegib, an orally administered inhibitor of the hedgehog signaling pathway, has also been shown to produce modest benefits in older adults considered ineligible for allogeneic HCT. When combined with low-dose cytarabine, AML patients over the age of 75 experienced a 4-month improvement in overall survival compared with those given low-dose cytarabine alone [18••]. However, low-dose cytarabine is no longer widely used and likely inferior to azanucleoside monotherapy [19]. Whether glasdegib improves treatment outcomes when combined with azacytidine or decitabine is currently not known.

Benefits of Drugs with Novel Delivery Mechanisms

CPX-351 is a drug that provides prolonged exposure to cytarabine and daunorubicin in a synergistic 5:1 ratio through liposomal delivery. This unique delivery mechanism may lead to decreased drug clearance and increased uptake into leukemic cells [20, 21]. Initial clinical trials enrolled older adults (age 60–75) with newly diagnosed AML and compared CPX-351 to traditional 7 + 3 IC. While no survival benefit was noted in the overall study population, a pre-planned subset analysis did reveal a survival benefit among those with secondary AML [22••]. A subsequent phase 3 trial enrolling only patients with secondary AML (antecedent myelodysplastic syndrome [MDS], chronic myelomonocytic leukemia [CMML], MDS-related cytogenetic abnormalities, or prior exposure to cytotoxic therapy) found a significantly higher CR rate (47.7% vs. 33.3% $p = 0.016$) and overall survival rate (9.56 vs. 5.95 months, $p = 0.005$) for those treated in the experimental arm [22••]. Based on these results, CPX-351 was approved as frontline therapy for treatment-related AML and AML with myelodysplasia-related changes in 2017.

GO, which consists of an anti-CD33 antibody conjugated to a toxic calicheamicin derivative, has recently re-emerged as a therapeutic option for CD33+ AML patients after a large meta-analysis of data from five randomized trials demonstrated that addition of GO to IC significantly reduced risk of relapse (HR 0.84 [0.76–0.92], $p = 0.0003$) and improved overall survival (HR 0.9 [0.82–0.98], $p = 0.01$) among patients with newly diagnosed AML. This was despite the fact that it did not increase the chances of achieving a CR or CR with incomplete peripheral count recovery. The effect on overall survival was particularly pronounced among those having favorable-risk cytogenetics [23••]. GO has now been included in the NCCN guidelines as an option in combination with standard induction therapy (7 + 3) for patients who have favorable- or intermediate-risk cytogenetics but also as monotherapy for those who cannot receive IC or who have relapsed/refractory disease [24]. The latter indication is largely based on data from the Mylo-France1 trial demonstrating a 33% response rate among patients with relapsed/refractory AML patients when the drug was given as a single agent [25].

Costs of Novel AML Therapies

The advent of novel therapeutics for AML may ultimately lead to improvements in outcome; however, this progress comes at a price. The indications, dosing recommendations, and average wholesale price (AWP) for each of these drugs are summarized in Table 1. Midostaurin, an oral drug that is given for 14 of 28 days during induction and consolidation [26], costs approximately $500–$600 (AWP) per day [27, 28•]. This equates to a cost of approximately $7500 (AWP) per induction and consolidation cycle [11••]. Gilteritinib, another drug recently approved for relapsed/refractory, FLT3-mutated AML, is given at a dose of 120 mg daily orally until progression or toxicity [29]. The AWP of gilteritinib is $300 per 40-mg tablet [27].

Both enasidenib and ivosidenib are oral medications that are given continuously until the time of progression or unacceptable toxicity [30, 31]. The cost of each 100-mg dose of enasidenib is approximately $1000 (AWP) [27]. A 500-mg daily dose of ivosidenib carries a similar AWP ($1044) [27]. Treatment with both drugs is recommended for a minimum of 6 months before declaring non-response, leading to a minimum drug cost of $200,000 (AWP) even in situations in which treatment ultimately fails.

Venetoclax and glasdegib are also orally administered and taken daily. Current estimates in the USA (largely based on its use in B cell malignancies) for the monthly AWP of venetoclax is approximately $10,000 [32] or > $100,000 per year [27]. Glasdegib is given for a minimum of 6 months before declaring treatment failure [18••]. Each daily dose carries an AWP of approximately $677 [27], which would equate to a cost of approximately $114,000 per 6 months of treatment.

Contrary to the other newly approved drugs, CPX-351 and GO are given as infusions. Specifically, CPX-351 is given as a single infusion on days 1, 3, and 5 [33] of induction therapy and each 44–100-mg vial costs approximately $9579 (AWP) [27]. This is followed by reinduction or consolidation infusions depending on patient response. A 4.5-mg vial of GO is a little less than $10,000 ($9840 [AWP]) [27]. It is recommended that a 3 mg/m^2 dose be given on days 1, 4, and 7 in combination with 7 + 3, as well as on day 1 of consolidation cycles. As monotherapy, it is dosed on days 1 (6 mg/m^2) and 8 (3 mg/m^2) of induction followed by a 3 mg/m^2 dose every 4 weeks during maintenance [34].

Table 1 Novel therapeutics in AML: clinical indications, dosing, and costs

Drug name (route of administration)	Indication	Dosing recommendations	Average wholesale price[δ]
Midostaurin (oral)	Newly diagnosed, FLT3-mutated AML in combination with 7 + 3 or HIDAC consolidation	50 mg twice daily, days 8–21 of induction and consolidation	$170.24 per 25-mg tablet
Gilteritinib (oral)	Relapsed/refractory FLT3-mutated AML	120 mg once daily	$300.00 per 40 mg
Enasidenib (oral)	Relapsed/refractory *IDH2*-mutated AML	100 mg once daily	$1029.79 per 100 mg
Ivosidenib (oral)	Relapsed/refractory *IDH1*-mutated AML	500 mg once daily	$522.30 per 250 mg
Venetoclax (oral)	Newly diagnosed AML in adults in whom IC is contraindicated—given in combination with azacytidine or decitabine	Day 1, 100 mg once daily Day 2, 200 mg once daily Day 3, 400 mg once daily Day 4 and beyond, 400 mg once daily	$11.15 per 10 mg $55.75 per 50 mg $111.51 per 100 mg
Glasdegib (oral)	Newly diagnosed AML in adults in whom IC is contraindicated—given in combination with LDAC	100 mg once daily	$338.50 per 25 mg
CPX-351 or liposomal daunorubicin and cytarabine (intravenous)	Newly diagnosed treatment-related AML or AML with myelodysplasia-related changes induction and consolidation	Induction, 44 mg/m^2–100 mg/m^2 on days 1, 3, 5 Reinduction (if patient not in remission), 44 mg/m^2–100 mg/m^2 days 1, 3 Consolidation, 29 mg/m^2–65 mg/m^2 on days 1 and 3 for 2 cycles	$9579.00 per 44–100-mg vial
Gemtuzumab ozogamicin (intravenous)	Newly diagnosed CD-33+ AML in combination with 7 + 3 Monotherapy for newly diagnosed CD-33+ AML in patients unsuitable for IC	Induction, 3 mg/m^2* on days 1, 4, 7 Consolidation, 3 mg/m^2* day 1 Induction, 6 mg/m^2 on day 1** then 3 mg/m^2 on day 8 Consolidation, 2 mg/m^2 day 1 every 4 weeks for maximum of 8 cycles	$9840.00 per 4.5-mg vial

[δ] Costs are reported as average wholesale price and are not meant to represent true costs as payer/institutional negotiations are not considered

[*] max 4.5 mg/dose

[**] no max dose

Complexities of Assessing Costs Versus Benefit in AML

The economics of caring for adult AML patients are highly complex, and the financial impact of these costly new drugs must be considered in this context. Regardless of drug costs, it has been previously demonstrated that the expense of treating AML is significant and largely driven by healthcare resource utilization [10, 35–39]. For instance, while standard chemotherapy for AML (e.g., 7 + 3 or high-dose cytarabine) is estimated to cost less than $2500 per treatment [40], administration of these regimens requires skilled nursing staff and at least a 5–7-day admission to the hospital. In addition, it is the current standard of care at most centers to follow induction chemotherapy with a 3–4-week hospital stay to monitor for disease- and treatment-related complications [41]. Supportive care for AML patients after IC adds significantly to the total inpatient costs [10, 40]. Even at centers where outpatient management after IC is available, readmissions are frequent and inpatient charges are rarely completely avoided [42]. In addition, intense outpatient monitoring, transfusion support, and antimicrobial prophylaxis are standard among those who achieve remission after IC or among patients receiving less aggressive treatments [35, 36]. Taking all of this into account, it is estimated that the cost of AML care among patients receiving IC ranges from $200,000 to 300,000 per year, exceeding $500,000 for those who undergo allogeneic HCT [10, 43]. Care of patients who are ineligible for IC is also expensive,

with one retrospective review of 237 AML patients finding a $27,756 per-patient per-month cost in the first year after diagnosis [44]. These large sums affect not only the healthcare system at large but may also lead to financial hardship and high-stress burden among AML patients [45].

It is therefore important to judge the cost-benefit of new AML treatments not only by the clinical benefit they may provide but also by how they will affect the downstream costs of AML care. Due to the novelty and lack of randomized trial data available for most of the drugs discussed in this article, very few budget impact and cost-effectiveness analyses are currently available. However, for drugs that have been evaluated in randomized trials, attempts have been made to examine their cost-effectiveness within the broad context of AML care. Some of these models use a societal perspective and take into account not only pharmaceutical costs but also the impact of new drugs on costs of other aspects of AML care, including inpatient and supportive care needs and importantly, potential shifts in the need for allogeneic HCT. The cost-effectiveness of midostaurin, for example, has been evaluated in combination with 7 + 3 from both the US payer and United Kingdom (UK) healthcare system perspectives [28•, 46•]. Both analyses found an overall rise in costs of care with the addition of midostaurin. However, this was driven not only by drug costs but also by an increase in the number of patients with *FLT3*-mutated AML receiving allogeneic HCT after responding to treatment. Ultimately, the potential survival benefit associated with the addition of midostaurin led both models to conclude that the drug is likely cost-effective [28•, 46•]. Similar studies are needed to assess the economic value of the other oral medications mentioned in this review, but this will likely not happen until phase III data are reported.

Special consideration should also be given to the impact of newer therapeutics on out-of-pocket costs and indirect costs related to lost work and income for patients and families, which have not historically been included in traditional cost-effectiveness analyses and economics models. The increasing use of oral oncology drugs may expose patients to higher out-of-pocket spending, particularly given the sharp rise in tiered prescription formularies in which expensive specialty oral drugs are often associated with the highest cost sharing. Few studies have focused on the out-of-pocket and indirect cost burden in adult AML patients; however, in chronic myeloid leukemia (CML), a disease in which oral oncology drugs predominate, high out-of-pocket costs are associated with poorer treatment adherence and lower health-related quality of life [47–50]. Future research should focus on the patient financial burden of new oral AML drugs and potential disparities in drug access, adherence, and subsequent outcome.

CPX-351 and GO are both given as infusions. The simplified administration schedule of CPX-351 may negate the need for the hospitalization required to administer standard 7 + 3. Thus, while CPX-351 carries a significant price tag, cost-benefit analyses suggest that the movement from inpatient to outpatient administration may lessen the impact on US payers [51]. One industry-sponsored budget impact analysis found that the incorporation of CPX-351 would have negligible financial impact, in large part because increased drug costs were offset by a reduction in inpatient time [51]. Another model predicted the increased efficacy of CPX-351 in treatment-related and myelodysplasia-related AML will likely drive its cost-effectiveness, with gains in quality-adjusted life-years offsetting the costs of the drug and increased number of allogeneic HCTs [52]. In a budget impact analysis of GO, improved efficacy led to theoretical reductions in relapses and reduced the need for allogeneic HCTs in patients with low- or intermediate-risk cytogenetics. These cost savings balanced drug costs in the model and ultimately projected minimal financial impact on US payers [53].

Table 2 Important considerations in cost-effectiveness of new AML agents

•Drug costs
•Chronicity of administration
•Increased survival time, quality of life years attained
•Reduction in resource utilization (e.g., transfusions, antibiotics) as more patients achieve CR
•Shift from inpatient to outpatient administration
•Reduced vs. increased costs from allogeneic stem cell transplantation
•Direct costs to healthcare system vs. patients

Conclusion

It is exciting to practice in a time when novel therapeutics are providing new hope to AML patients. As knowledge regarding the underlying mechanisms of the disease expands, it is expected that additional drugs will receive regulatory approval in the near future. However, for many of the drugs approved in the last 2 years, results of phase III trials have yet to be reported, making it difficult to assess their true clinical impact at this time. It also cannot be ignored that these potential clinical benefits will likely come at a substantial price, as has been seen with the development of other novel therapies for hematologic malignancies [9, 54]. This issue warrants close attention. The American Association of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) have recently devised methodologies to help clinicians assess the "value" of various cancer treatments and provide guidance in decision-making about patient care [55•, 56]. These

assessments weigh the affordability and cost of a particular treatment not only against efficacy outcomes (i.e., remission rates, duration of remission, overall survival benefit) but also how achievement of these goals may translate to improvement in the quality of life and cost reduction by leading to symptom relief and treatment-free intervals. For AML, the ultimate economic value of new drugs will be determined by these variables in addition to considering the larger, but perhaps more indirect impact they may have on the use of healthcare resources (Table 2). Given the novelty of many of the drugs reviewed in this article, it may be some time before in-depth cost-benefit analyses are available to provide evidence of their economic value, and these future studies must be comprehensive in their approach. Among the few drugs for which phase 3 results are available, initial cost-effectiveness assessments appear to be favorable. Incorporation of data collection on health-related quality of life and financial toxicity into future randomized trials evaluating all of the novel AML agents could further strengthen the evidence of their economic value. Strategies such as these will ensure that the excitement of new discovery does not distract us from constantly monitoring the economic impact of AML care as we see more and more novel therapeutics come to market.

Acknowledgments R.B.W. is a Leukemia & Lymphoma Society Scholar in Clinical Research.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. N Engl J Med. 2015;373(12):1136–52. https://doi.org/10.1056/NEJMra1406184.
2. Deschler B, de Witte T, Mertelsmann R, Lübbert M. Treatment decision-making for older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia: problems and approaches. Haematologica. 2006;91(11):1513–22.
3. O'Donnell MR, Tallman MS, Abboud CN, Altman JK, Appelbaum FR, Arber DA, et al. Acute myeloid leukemia, version 3.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(7):926–57. https://doi.org/10.6004/jnccn.2017.0116.
4. Döhner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Büchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424–47. https://doi.org/10.1182/blood-2016-08-733196.
5. Krok-Schoen JL, Fisher JL, Stephens JA, Mims A, Ayyappan S, Woyach JA, et al. Incidence and survival of hematological cancers among adults ages >/=75 years. Cancer Med. 2018;7:3425–33. https://doi.org/10.1002/cam4.1461.
6. Bailey C, Richardson LC, Allemani C, Bonaventure A, Harewood R, Moore AR, et al. Adult leukemia survival trends in the United States by subtype: a population-based registry study of 370,994 patients diagnosed during 1995-2009. Cancer. 2018;124(19):3856–67. https://doi.org/10.1002/cncr.31674.
7. Lichtman MA. A historical perspective on the development of the cytarabine (7days) and daunorubicin (3days) treatment regimen for acute myelogenous leukemia: 2013 the 40th anniversary of 7+3. Blood Cells Mol Dis. 2013;50(2):119–30. https://doi.org/10.1016/j.bcmd.2012.10.005.
8. Allen PB, Flowers CR. Balancing patient value and payer cost in hematologic malignancies: can it be done? Expert Rev Pharmacoecon Outcomes Res. 2018;18(2):123–6. https://doi.org/10.1080/14737167.2018.1444478.
9. Saret CJ, Winn AN, Shah G, Parsons SK, Lin PJ, Cohen JT, et al. Value of innovation in hematologic malignancies: a systematic review of published cost-effectiveness analyses. Blood. 2015;125(12):1866–9. https://doi.org/10.1182/blood-2014-07-592832.
10. Mahmoud D, Skikne BS, Kucmin-Bemelmans I, Alleman C, Hensen M. Overall economic burden of total treatment costs in acute myeloid leukemia throughout the course of the disease. Blood [Internet]. 2012 [cited 2019 Apr 23];120(21):3614. Available from: http://www.bloodjournal.org/content/120/21/3614?ssochecked=true.
11. •• Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454–64. https://doi.org/10.1056/NEJMoa1614359 **Phase 3 trial that demonstrated surival benefit when midostaurin added to 7+3 in FLT3-mutated AML. Led to approval of midostaurin in frontline treatment of FLT3-mutated AML.**
12. U.S. Food & Drug Administration. FDA approves gilteritinib for relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation. 2018. [cited 2019 Apr 23]. Available from: https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm627045.htm.
13. Patel KP, Ravandi F, Ma D, Paladugu A, Barkoh BA, Medeiros LJ, et al. Acute myeloid leukemia with IDH1 or IDH2 mutation: frequency and clinicopathologic features. Am J Clin Pathol. 2011;135(1):35–45. https://doi.org/10.1309/AJCPD7NR2RMNQDVF.
14. • Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood. 2017;130(6):722–31. https://doi.org/10.1182/blood-2017-04-779405 **Phase 1/2 study demonstrating efficacy of venetoclax in combination with low-dose cytarabine among AML patients ineligible for intensive chemotherapy.**
15. • DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med. 2018;378(25):2386–98. https://doi.org/10.1056/NEJMoa1716984 **Phase 1b dose escalation and expansion study suggesting safety and efficacy of venetoclax in combination with hypomethylating agents in treatment-naïve AML among patients ineligible for intensive chemotherapy.**

16.• Wei AH, Strickland SA, Roboz GJ, Hou JZ, Fiedler W, Lin TL, et al. Safety and efficacy of venetoclax (VEN) plus low-dose cytarabine (LDAC) in treatment-naive patients (PTS) aged >= 65 years with acute myeloid leukemia (AML). Ann Hematol. 2017;96: S85-S **Phase 1/2 study demonstrating efficacy of venetoclax in combination with low-dose cytarabine among AML patients ineligible for intensive chemotherapy.**

17.• DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7–17. https://doi.org/10.1182/blood-2018-08-868752 **Phase 1b dose escalation and expansion study suggesting safety and efficacy of venetoclax in combination with hypomethylating agents in treatment- naïve AML among patients ineligible for intensive chemotherapy.**

18.•• Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. Leukemia. 2018. 9;33(2):379–1389. https://doi.org/10.1038/s41375-018-0312-9. **Randomized trial demonstrating a 4-month survival benefit among elderly patients treated with glasdegib in combination with low-dose cytarabine vs. low-dose cytarabine.**

19. Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. Blood. 2015;126(3):291–9. https://doi.org/10.1182/blood-2015-01-621664.

20. Feldman EJ, Lancet JE, Kolitz JE, Ritchie EK, Roboz GJ, List AF, et al. First-in-man study of CPX-351: a liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio for the treatment of relapsed and refractory acute myeloid leukemia. J Clin Oncol. 2011;29(8):979–85. https://doi.org/10.1200/JCO.2010.30.5961.

21. Wei AH, Tiong IS. Midostaurin, enasidenib, CPX-351, gemtuzumab ozogamicin, and venetoclax bring new hope to AML. Blood. 2017;130(23):2469–74. https://doi.org/10.1182/blood-2017-08-784066.

22.•• Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol. 2018;36(26):2684–92. https://doi.org/10.1200/JCO.2017.77.6112 **Randomized study of CPX-351 vs. 7 + 3 among patients with newly diagnosed secondary acute myeloid leukemia demonstrating survival benefit.**

23.•• Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol. 2014;15(9):986–96. https://doi.org/10.1016/S1470-2045(14)70281-5 **Meta-analysis demonstrating reduced risk of relapse and improved survival among patients with newly diagnosed AML treated with GO in addition to induction chemotherapy.**

24. Network NCC. Acute Myeloid Leukemia 1.2019. 2018. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf. Accessed January 21, 2019.

25. Taksin AL, Legrand O, Raffoux E, de Revel T, Thomas X, Contentin N, et al. High efficacy and safety profile of fractionated doses of Mylotarg as induction therapy in patients with relapsed acute myeloblastic leukemia: a prospective study of the alfa group. Leukemia. 2007;21(1):66–71. https://doi.org/10.1038/sj.leu.2404434.

26. Rydapt (midostaurin) [prescribing information]. East Hanover: NJ: Novartis Pharmaceuticals Corporation. 2018.

27. ™ L. LexiDrugs Walters Kluwer Health, Inc, uptodate.com. Accessed January 30 2019.

28.• Stein E, Xie J, Duchesneau E, Bhattacharyya S, Vudumula U, Ndife B, et al. Cost effectiveness of midostaurin in the treatment of newly diagnosed flt3-mutated acute myeloid leukemia in the United States. Pharmacoeconomics. 2019;37(2):239–53. https://doi.org/10.1007/s40273-018-0732-4 **Cost-effectivness evaluation of midostaurin in the treatment of newly diagnosed FLT3-mutated AML.**

29. Xospata (gilteritinib) [prescribing information]. Northbrook: Astellas Pharma US, Inc. 2018.

30. Idhifa (enasidenib) [prescribing information]. Summit: Celgene Corporation. 2017.

31. Tibsovo (ivosidenib) [prescribing information]. Cambridge: Agios Pharmaceuticals, Inc. 2018.

32. Savage P. Approvals in 2016: cost-benefit challenges of new anticancer agents. Nat Rev Clin Oncol. 2017;14(3):133–4. https://doi.org/10.1038/nrclinonc.2017.12.

33. Vyxeos (daunorubicinand cytarabine [liposomal]) [prescribing information]. Jazz Pharmaceuticals Inc. 2017.

34. Mylotarg (gemtuzumab ozogamicin) [prescribing information]. Philadelphia: Wyeth Pharmaceuticals. 2018.

35. Bosshard R, O'Reilly K, Ralston S, Chadda S, Cork D. Systematic reviews of economic burden and health-related quality of life in patients with acute myeloid leukemia. Cancer Treat Rev. 2018;69:224–32. https://doi.org/10.1016/j.ctrv.2018.07.005.

36. Menzin J, Lang K, Earle CC, Kerney D, Mallick R. The outcomes and costs of acute myeloid leukemia among the elderly. Arch Intern Med. 2002;162(14):1597–603.

37. Redaelli A, Botteman MF, Stephens JM, Brandt S, Pashos CL. Economic burden of acute myeloid leukemia: a literature review. Cancer Treat Rev. 2004;30(3):237–47. https://doi.org/10.1016/j.ctrv.2003.11.002.

38. Nerich V, Lioure B, Rave M, Recher C, Pigneux A, Witz B, et al. Induction-related cost of patients with acute myeloid leukaemia in France. Int J Clin Pharm. 2011;33(2):191–9. https://doi.org/10.1007/s11096-010-9462-1.

39. Leunis A, Blommestein HM, Huijgens PC, Blijlevens NM, Jongen-Lavrencic M, Uyl-de Groot CA. The costs of initial treatment for patients with acute myeloid leukemia in the Netherlands. Leuk Res. 2013;37(3):245–50. https://doi.org/10.1016/j.leukres.2012.09.018.

40. Fedele PL, Avery S, Patil S, Spencer A, Haas M, Wei A. Health economic impact of high-dose versus standard-dose cytarabine induction chemotherapy for acute myeloid leukaemia. Intern Med J. 2014;44(8):757–63. https://doi.org/10.1111/imj.12478.

41. Walter RB, Taylor LR, Gardner KM, Dorcy KS, Vaughn JE, Estey EH. Outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia. Clin Adv Hematol Oncol. 2013;11(9):571–7.

42. Vaughn JE, Othus M, Powell MA, Gardner KM, Rizzuto DL, Hendrie PC, et al. Resource utilization and safety of outpatient management following intensive induction or salvage chemotherapy for acute myeloid leukemia or myelodysplastic syndrome: a nonrandomized clinical comparative analysis. JAMA Oncol. 2015;1(8):1120–7. https://doi.org/10.1001/jamaoncol.2015.2969.

43. Preussler JM, Meyer CL, Mau LW, Majhail NS, Denzen EM, Edsall KC, et al. Healthcare costs and utilization for patients age 50 to 64 years with acute myeloid leukemia treated with chemotherapy or with chemotherapy and allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant. 2017;23(6):1021–8. https://doi.org/10.1016/j.bbmt.2017.02.017.

44. Bell JA, Galaznik A, Farrelly E, Blazer M, Murty S, Ogbonnaya A, et al. Economic burden of elderly patients with acute myeloid leukemia treated in routine clinical care in the United States. Leuk Res. 2018;71:27–33. https://doi.org/10.1016/j.leukres.2018.06.010.

45. Knight TGRM, Bohannon L, Blackwell E, Ai J, Ragon B, Davis R, et al. Patient reported financial toxicity in acute leukemia. Blood. 2018;132(Suppl 1):4796. https://doi.org/10.1182/blood-2018-99-119163.
46.• Tremblay G, Dolph M, Patel S, Brandt P, Forsythe A. Cost-effectiveness analysis for midostaurin versus standard of care in acute myeloid leukemia in the United Kingdom. Cost Eff Resour Alloc. 2018;16:33. https://doi.org/10.1186/s12962-018-0153-4 **Cost-effectiveness analysis evaluating addition of midostaurin to 7 + 3 in treatment of newly diagnosed FLT3-mutated AML.**
47. Shen C, Zhao B, Liu L, Shih YT. Adherence to tyrosine kinase inhibitors among Medicare Part D beneficiaries with chronic myeloid leukemia. Cancer. 2018;124(2):364-73. https://doi.org/10.1002/cncr.31050.
48. Jiang Q, Wang H, Yu L, Gale RP. Higher out-of-pocket expenses for tyrosine kinase-inhibitor therapy is associated with worse health-related quality-of-life in persons with chronic myeloid leukemia. J Cancer Res Clin Oncol. 2017;143(12):2619-30. https://doi.org/10.1007/s00432-017-2517-0.
49. Shen C, Zhao B, Liu L, Shih YT. Financial Burden for Patients With Chronic Myeloid Leukemia Enrolled in Medicare Part D Taking Targeted Or al Anticancer Medications. J Oncol Pract. 2017;13(2):e152-e62. https://doi.org/10.1200/JOP.2016.014639.
50. Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. J Clin Oncol. 2014;32(4):306-11. https://doi.org/10.1200/JCO.2013.52.9123.
51. Jensen IS, Wu E, Sacks NC, Cyr PL, Chung KC. Budget impact analysis of using daunorubicin-cytarabine liposome in patients with newly diagnosed therapy-related AML or AML and myelodysplasia-related changes. Am Health Drug Benefits. 2018;11(7):380–6.
52. Kansal A, Du M, Herrera-Restrepo O, Leipold R, Ryan RJ, Louie AC, et al. Cost-effectiveness of CPX-351 versus 7+3 regimen in the treatment of treatment-related acute myeloid leukemia (tAML) or AML with myelodysplasia-related changes (MRC). Blood [Internet]. 2017 [cited 2019 Apr 23];130(Suppl 1):4674. https://www.bloodjournal.org/content/130/Suppl_1/4674.
53. Walter RB, Mamolo C, Welch V, Brockbank J, Cawson M, Knight C, Wilson M. Budget impact analysis for gemtuzumab ozogamicin in CD 33+ acute myeloid leukemia. World Congress of the International Society of Hematology 2. Presented at the XXXVII World Congress of the International Society of Hematology (ISH), September 13–16, 2018; Vancouver, Canada.
54. Chen Q, Jain N, Ayer T, Wierda WG, Flowers CR, O'Brien SM, et al. Economic burden of chronic lymphocytic leukemia in the era of oral targeted therapies in the United States. J Clin Oncol. 2017;35(2):166–74. https://doi.org/10.1200/JCO.2016.68.2856.
55.• Schnipper LE, Davidson NE, Wollins DS, Blayney DW, Dicker AP, Ganz PA, et al. Updating the American Society of Clinical Oncology Value Framework: revisions and reflections in response to comments received. J Clin Oncol. 2016;34(24):2925–34. https://doi.org/10.1200/jco.2016.68.2518 **Budget impact analysis evaluating addition of CPX 351 in treatment of adults with newly diagnosed secondary AML.**
56. Carlson RW, Jonasch E. NCCN Evid Blocks. 2016;14(5S):616–9. https://doi.org/10.6004/jnccn.2016.0177.