

Unmet Clinical Needs and Economic Burden of Disease in the Treatment Landscape of Acute Myeloid Leukemia

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Background

Acute myeloid leukemia (AML) poses a substantial clinical burden worldwide. In 2012, more than 350,000 individuals were diagnosed with leukemia globally, including chronic and acute lymphoid and myeloid leukemias.¹ AML is the most common form of acute leukemia in adults in the United States, with approximately 19,520 new cases estimated for 2018.² Cancer statistics from Surveillance, Epidemiology, and End Results demonstrate a trend toward a rise in the number of new cases of AML diagnosed each year, with an increase in incidence of 3.43 to 4.26 per 100,000 from 1975 to 2015.³ The increases in overall incidence of AML may be due, in part, to a growing population of older individuals, because the likelihood of AML increases with age.³ Additionally, an improved awareness of the presenting features of AML, improvements in diagnostic ability, and an increased willingness to work up and consider therapy in older patients with AML may be contributing to the increased incidence.⁴ Although the incidence of AML is highest among individuals 65 years and over, more than 43% of newly diagnosed patients with AML are younger than 65 years.³ In the population younger than 65, the incidence of AML is 2 per 100,000 individuals, compared with 20.1 per 100,000 individuals 65 years or older.³

Despite recent advances in the management of patients with hematologic malignancies, such as the development of novel and effective targeted and immune therapies and improvements in supportive care measures, the overall survival outcomes for patients with AML remain poor. The 5-year relative survival rate in patients with AML who are younger than 65 is approximately 45%.³ Moreover, this number likely overestimates survival in patients aged 45 to 65 years because the 5-year relative survival rate for patients younger than 45 years is 59.5% (Table 1).³ As patients age, the 5-year relative survival rates decline rapidly. This is partially explained by the increased likelihood of favorable cytogenetic profiles, such as t(8;21), inv(16) and t(15;17), seen in younger patients. Young patients are not only more likely to have favorable cytogenetics, they are also more likely to experience better outcomes relative to their cytogenetic- and treatment-matched older counterparts because of better organ function and lower rates of comorbidities.⁵

ABSTRACT

Acute myeloid leukemia (AML) is the most common form of acute leukemia in adults in the United States, with approximately 19,520 new cases estimated for 2018. Despite advances in the management of hematologic malignancies, the development of novel targeted and immune therapies, and improvements in supportive care, the overall outcome for patients with AML remains poor due to several factors, including increased frequency in the older population, poor response to chemotherapy, high relapse rates, and limited effective therapy options in relapsed patients. In addition, AML presents a substantial clinical and financial burden attributable in part to the heterogenic characteristics at presentation, such as varied age distributions and cytogenetic and molecular abnormalities, coupled with prolonged hospitalizations, high rates of infectious complications, and need for allogeneic stem cell transplants. Several unmet needs exist in AML. For instance, more-effective, less-toxic treatments are urgently needed because many patients with AML are not candidates for standard induction therapy. AML is also characterized by high rates of relapsed/refractory disease; therefore, strategies to reduce relapse are important. Other unmet needs center on poor quality of life from disease- and therapy-related toxicities and inadequate psychosocial support frequently experienced by many patients with AML and by their caregivers. This review will discuss these issues and additional challenges faced both by patients with AML and by caregivers and medical personnel who work in the AML setting.

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TABLE 1. Five-Year Relative Survival Rates by Age at Diagnosis of Acute Myeloid Leukemia³

Age at diagnosis (years)	Both Sexes	Male Patients	Female Patients
<45	59.5%	57.4%	61.6%
45-54	42.1%	40.9%	43.4%
55-64	29.6%	28.0%	31.8%
65-74	12.7%	12.1%	13.7%
≥75	3.0%	3.2%	2.7%

Poor outcomes in AML are related to several factors, including the presence of concomitant comorbidities or organ dysfunction preventing patients from receiving optimal chemotherapy regimens, the expression of high-risk features such as adverse karyotypes and mutations, and an increased risk of second primary malignancies (SPMs).⁵⁻⁷ There are several approaches to the treatment of AML, which include chemotherapy, targeted therapy, immunotherapy, and hematopoietic stem cell transplantation (HSCT). Treatment challenges are largely associated with primary and secondary resistance to therapeutic agents. Treatment-resistant disease or relapsed disease is associated with decreased overall survival (OS). Continued poor outcomes paired with an increase in the number of newly diagnosed AML cases suggests that AML is a disease that represents an increasing economic burden.

Prognostic Assessments

AML is a heterogeneous disorder with regard to morphology, including, but not limited to, chromosome and molecular aberrations detected in the leukemic cells.⁸ Different subtypes of AML may have distinct causal mechanisms, suggesting functional links among specific molecular abnormalities and mutations and the presumed causal agents.⁹ Although most cases of AML arise de novo, environmental factors, such as prolonged exposure to paints, benzene, alcohol, tobacco, or other chemical toxins, may be associated with AML pathogenesis in a small minority of cases. Previous cytotoxic or radiation therapy and the presence of antecedent hematologic conditions, such as myelodysplastic syndrome or myeloproliferative neoplasms, are known to increase the incidence of AML and are associated with poorer prognosis than for patients who develop AML de novo.^{9,10}

Chromosomal abnormalities are found in the majority of patients with AML.¹¹ Frequent cytogenetic abnormalities include loss or deletion of chromosome 5, 7, 17, and Y; translocations such as t(8;21), t(15;17), and trisomy 8 and 21; and other abnormalities involving chromosomes 1, 3, 9, 11, and 16.^{8,11-13} The cytogenetic landscape of AML is further complicated by the fact that these abnormalities occur at different frequencies in different age groups and in de novo versus secondary AML.^{11,12}

Multiple studies have demonstrated the prognostic importance of cytogenetic abnormalities in AML as predictors of response and OS as well as a useful tool to guide treatment (Table 2¹²⁻¹⁶).^{8,11-13,17} According to multiple large studies, patients with t(8;21), inv(16)/t(16;16), and del(9q) tend to have significantly better outcomes, whereas patients with inv(3)/t(3;3), -5/5q-, -7, loss of 7q, +8, abn(12p), -17/17p-, -18, -20, and loss of 20q tend to have significantly poorer outcomes.^{5,8,12,13,17} Furthermore, patients with t(8;21) and inv(16)/t(16;16) had a significantly improved chance of 5-year survival and relapse-free survival compared with patients with a normal karyotype.⁸ Aside from aiding in predicting outcomes in AML, cytogenetics may help guide treatment, suggesting that cytogenetic profiling should be performed in all newly diagnosed patients with AML.

Traditionally, AML classification and risk stratification relied predominantly on cytogenetic studies. However, in the past decade the molecular detection of gene mutations has become an increasingly important tool for classification, risk stratification, and management of patients with AML. Molecular analysis plays a complementary role to cytogenetic testing by helping further refine prognosis, especially within specific AML subgroups such as patients with intermediate or diploid cytogenetics. In addition to their role as a prognostic tool, some molecular abnormalities have emerged as potential therapeutic targets.¹⁸ Some of the most important AML-related gene mutations include transcription-factor fusion genes; *NPM1*, *RUNX1*, *TP53*, and *CEBPA*, *FLT3* mutations (both ITD and D835); other tyrosine kinases, serine-threonine kinases, protein tyrosine phosphatases; and *RAS* family protein mutations, mutations in *IDH1/2*, and mutations in *DNMT3A*, *ASXL1*, *RUNX1*, and *PTPN11*.¹⁸ Mutations in these AML-related genes can co-occur (ie, mutations either in *NPM1* and *DNMT3A* or in *NPM1* and *FLT3*) or can be mutually exclusive (ie, mutations in *RUNX1* and *TP53* are frequently mutually exclusive of *FLT3* and *NPM1* mutations). Based on these mutations, researchers and physicians have identified subtypes of AML with significant differences in prognosis and treatment.^{18,19} Although mutational aberrations may be distinct from epigenetic aberrations, they often interact with each other to determine prognosis, as demonstrated in patients with AML with *IDH1/2* mutations.²⁰ Several reviews have described the prognostic significance of cytogenetic and molecular markers associated with AML, and those in younger adults are outlined in Table 3.^{12,14-16}

Current Standards of Care in AML

The treatment of AML is divided into 2 phases: remission induction and consolidation. Remission induction with chemotherapy aims to reduce the leukemic burden and restore normal hematopoiesis to produce complete remission (CR). Although most patients will achieve CR after induction therapy, 50% to 60% of patients with AML will experience disease recurrence if treatment is discontinued after induction.²¹ Therefore, a favorable response to

induction therapy should be followed by consolidation therapy, usually composed of intermediate- or high-dose cytarabine-based therapy or alloHSCT, to eradicate residual disease (detectable or nondetectable) and aid in achieving lasting remission.

Induction Therapy

Cytarabine and an anthracycline-based induction has remained the standard of care for patients with AML for the past 4 decades.^{19,22} The most frequently used iteration of the cytarabine and anthracycline combination has been the “7 + 3” regimen, which includes a 7-day continuous infusion of cytarabine at the dosage of 100 or 200 mg/m² per day on days 1 to 7 and 12 mg/m² idarubicin or 45 to 60 mg/m² daunorubicin on days 1 to 3. Several studies have evaluated the comparative benefits of anthracycline dose escalation in the 7 + 3 regimen to improve CR and survival outcomes; benefits varied by age and molecular and cytogenetic risk profiles.

Intensification of the daunorubicin dose during induction therapy was investigated in patients aged 17 to 60 years with previously untreated AML (N = 657). In the total patient population, treatment with 90 mg/m² daunorubicin daily for 3 days in combination with 100 mg/m² of cytarabine for 7 days significantly improved median OS compared with standard-dose daunorubicin (45 mg/m²) (23.7 vs 15.7 months; *P* = .003) used in the 7 + 3 regimen. The high-dose treatment group also experienced a higher rate of CR than those with standard-dose daunorubicin treatment (70.6% vs 57.3%; *P* < .001). Age and molecular and cytogenetic risk were significant determinants of survival benefit and CR with high-dose daunorubicin. Patients younger than 50 years achieved a CR rate of 59.4% and a median survival of 19 months with the standard dose, compared with a CR rate of 74.3% and median survival of 34.3 months with the high dose (*P* = .004). CR rates for the favorable-risk, intermediate-risk, and unfavorable-risk cytogenetic subgroups were 81.3%, 58.7%, and 51.4%, respectively (*P* < .001 for overall comparisons). Patients with favorable and intermediate cytogenetic risk experienced longer median survival and higher CR rates with high-dose daunorubicin. In this study, treatment with high-dose daunorubicin did not provide improved survival in patients older than 50 years or those with unfavorable cytogenetic risk.²³ In contrast, in another study with patients (N = 813) aged 60

to 83 years who were administered cytarabine at 200 mg/m²/day by continuous infusion for 7 days plus daunorubicin for 3 days at either the conventional dose of 45 mg/m²/day or the escalated dose of 90 mg/m²/day, high-dose daunorubicin was associated with a significantly higher CR rate than the conventional dose (64% vs 54%; *P* = .002). Patients treated with high-dose daunorubicin were more likely to achieve CR after the first induction cycle (52% vs 35%; *P* < .001). In this study, the greatest disease-free survival (DFS) benefit and CR rate improvement with high-dose daunorubicin treatment compared with standard-dose treatment were demonstrated in the youngest cohort of patients enrolled (patients aged 60-65 years) and those with favorable cytogenetic risk.²⁴

Intensification of the anthracycline dose of 7 + 3 with daily daunorubicin (80 mg/m²) was compared with standard doses of idarubicin (12 mg/m²) in patients with AML aged 50 to 70 years. Intensified daunorubicin was less likely to induce CR than standard-dose idarubicin (70% vs 83%; *P* = .04), with no difference in the event-free survival (EFS) or OS.²⁵ To date, dose escalation of anthracyclines has yet to receive a firm recommendation.¹⁹

TABLE 2. Clinically Significant Cytogenetic and Molecular Characteristic Indicators of Prognostic Risk in Patients With Acute Myeloid Leukemia¹²⁻¹⁶

Classification	Subsets
Favorable	<ul style="list-style-type: none"> • t(8;21)(q22;q22)/ <i>RUNX1-RUNX1T1</i> • inv(16)(p13.1q22)/t(16;16)(p13.1;q22)/<i>CBFB-MYH11</i> • Mutated <i>NPM1</i> without <i>FLT3-ITD</i> or <i>DNMT3A</i> mutations (normal karyotype) • t(15;17)(q22;q21)/<i>PML-RARA</i> • Biallelic <i>CEBPA</i> mutation
Intermediate	<ul style="list-style-type: none"> • Mutated <i>NPM1</i> and <i>FLT3-ITD</i>^{high,a} (normal karyotype) • Wild-type <i>NPM1</i> and <i>FLT3-ITD</i>^{low,a} (normal karyotype) • Wild-type <i>NPM1</i> without <i>FLT3-ITD</i> (normal karyotype) • t(8;21) or inv(16) with <i>KIT</i> mutation • t(9;11)(p21.3;q23.3); <i>MLLT3-KMT2A</i> • Cytogenetic abnormalities not classified as favorable or adverse
Adverse	<ul style="list-style-type: none"> • inv(3)(q21q26.2)/ t(3;3)(q21;q26.2)/ <i>RPN1-EVI1</i> • t(6;9)(p23;q34)/ <i>DEK-NUP214</i> • t(v;11)(v;q23)/ <i>MLL</i> rearranged • t(9;22)(q34.1;q11.2)/ <i>BCR-ABL1</i> • t(11q23) abnormalities other than t(9;11) • Wild-type <i>NPM1</i> and <i>FLT3-ITD</i>^{high} • <i>DNMT3A</i> mutations • Mutated <i>RUNX1</i> • Mutated <i>ASXL1</i> • Mutated <i>TP53</i> • -5 or del(5q) • -7 or del(7q) • -17, 17p abnormalities • Complex karyotype

ABL1 indicates ABL proto-oncogene 1; ASXL, sex combs-like 1; CBFB, core-binding factor bBeta subunit; CEBPA, CCAAT/enhancer binding protein alpha; DEK, DEK proto-oncogene; FLT3, fms-like tyrosine kinase 3; ITD, internal tandem duplication; KIT, KIT proto-oncogene receptor tyrosine kinase; MLLT3, super elongation complex subunit; MYH11, myosin heavy chain 11; NPM1, nucleophosmin 1; NUP214, nucleoporin 214; RPN1, ribophorin I; RUNX1, runt-related transcription factor 1; RUNX1T1, RUNX1 translocation partner 1; TP53, tumor protein 53.

^a Determined *FLT3-ITD* allelic ratio using DNA fragment analysis. Low indicates low allelic ratio (<0.5); high indicates high allelic ratio (>0.5).

TABLE 3. Clinically Significant Cytogenetics in Patients With Acute Myeloid Leukemia (AML): Select Molecular and Cytogenetic Prognostic Indicators of Prognostic Risk in Younger Patients (16 to 60 Years) With AML^{12,14-16}

Molecular or Cytogenetic Biomarker	Prevalence (presented in patients aged 16 to 60 years)	Prognostic Implication
<i>DNMT3A</i>	20%	Adverse risk Associated with normal karyotypes, <i>NPM1</i> , <i>FLT3</i> -ITD <i>DNMT3A</i> mutations are in progenitor cells and are present in early leukemogenesis; may persist after therapy, lead to clonal expansion during remission, and cause recurrent disease
<i>NPM1</i>	33%	Adverse in wt- <i>NPM1</i> and <i>FLT3</i> -ITD Favorable risk in mutated <i>NPM1</i> without <i>FLT3</i> -ITD or with <i>FLT3</i> -ITD
<i>TP53</i>	8%	Associated with complex karyotype, monosomal karyotype, and specific chromosomal aneuploidies (25/−5q, 27/−7q, 217/17p) Predicts adverse and very poor outcomes
<i>FLT3</i> -ITD	27%	Poor in intermediate-risk AML; independent predictor of higher relapse and poor overall survival in <i>FLT3</i> -ITD ^{high}
<i>IDH2</i>	<i>IDH2</i> -R172: 2% <i>IDH2</i> -R140: 7%	Both associated with normal karyotypes R172 Adverse R140 Favorable
<i>IDH1</i>	7%	Associated with <i>FLT3</i> -ITD; adverse prognostic outcome

AML indicates acute myeloid leukemia; DNMT3A, DNA [cytosine-5]-methyltransferase 3A; FLT3, fms-like tyrosine kinase 3; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; ITD, internal tandem duplication; NPM1, nucleophosmin 1; TP53, tumor protein 53; wt, wild-type.

Several studies have investigated the combination of 7 + 3 with new agents by adding a third drug to induction therapy. In a group of patients 60 years and younger, the addition of sorafenib, a multikinase inhibitor, did not increase the likelihood of CR but significantly increased EFS and relapse-free survival (RFS), with a trend for improved OS. The addition of sorafenib did not result in significantly increased early mortality rates or therapy discontinuation rates but was associated with an increased risk of fever, bleeding events, and hand-foot syndrome.²⁶ In another study of patients 60 years and older, the addition of sorafenib to 7 + 3 induction did not confer any significant benefit regarding CR, overall response rate, EFS, or OS. In this study, the addition of sorafenib was associated with an increased 60-day mortality, more deaths attributed to infections, and higher risk of infectious complications.²⁷

In a group of patients 60 years and younger, treatment with gemtuzumab ozogamicin (GO) demonstrated survival benefit based on cytogenetic risk; overall, patients with favorable-risk cytogenetics had the most clinically meaningful improvement in OS.²⁸ In a subsequent meta-analysis of 5 large randomized trials, GO improved OS most significantly in patients with favorable cytogenetics but also showed a significant improvement in OS in patients with intermediate cytogenetics.²⁹ In patients older than 60 years, GO did not increase likelihood of CR but showed significant benefit regarding cumulative incidence of relapse, RFS, and OS, a finding that was not restricted to any particular patient subset.³⁰ GO was approved

in the United States in 2017 for the treatment of newly-diagnosed CD33-positive AML in adults based on the ALFA-0701 study and for the treatment of relapsed/refractory (R/R) CD33-positive AML in patients 2 years and older based on the Mylofrance study results.^{31,32}

Consolidation Therapy

Consolidation therapy is used after patients have reached clinical and hematologic remission. The aim of consolidation therapy is to control disease remission after induction therapy. Consolidation therapy may involve chemotherapy alone, alloHSCT alone, or high-dose chemotherapy followed by alloHSCT. Because alloHSCT may offer a more favorable risk-benefit profile for patients who fall into the adverse-risk cytogenetic category than for those with favorable cytogenetics, chemotherapy is a reasonable first-line consolidation choice for patients with a favorable cytogenetic profile.³³ Currently, there is no consensus on a single “best” postremission treatment schedule. Generally, it is recommended that patients with a favorable risk classification, such as those with t(8;21)(q22;q22), inv(16)(p13.1q22), or t(16;16)(p13.1;q22), as well as patients who are unsuitable for alloHSCT, receive at least 3 to 4 cycles of intensive consolidation chemotherapy that uses intermediate- or high-dose cytarabine. No significant differences in survival (5-year OS or DFS) were demonstrated between intermediate (12 g/m²) and high-dose (36 g/m²) cytarabine, regardless of age or cytogenetic/molecular risk classifications. However, the risk of toxicity was different between

dose groups, wherein patients who received high-dose cytarabine took longer to recover neutrophil count to more than 500/uL and were more likely to have erythrocyte transfusions.³⁴ Mayer et al found that only 29% of patients older than 60 years could tolerate high-dose cytarabine, mostly because of hematologic toxicity and neurotoxicity, suggesting a need for less-intense treatments in older patients.³⁵

Generally, alloHSCT is not recommended in favorable-risk patients because risk of toxicity and/or transplantation-related mortality may exceed the benefit of the procedure. Specifically, the decision to perform alloHSCT depends on the assessment of the risk–benefit ratio (ie, nonrelapse mortality/morbidity vs reduction of relapse risk), which is based on cytogenetic and molecular genetic features at diagnosis, minimal residual disease status after induction and/or consolidation, and other patient-, donor-, and transplant-related characteristics, such as the patient’s age, comorbidities, organ function, and type of available donor. AlloHSCT is recommended when the relapse incidence without the procedure is expected to be more than 35% to 40%. Therefore, patients with intermediate- and adverse-risk AML may be considered for alloHSCT on a case-by-case basis. Elderly patients or patients with significant comorbidities may not be eligible for alloHSCT. Elderly patients who are not candidates for HSCT may be candidates for low-dose chemotherapy, which may include either low-dose cytarabine or hypomethylating agent (eg, decitabine or azacitidine)–based therapy.¹⁶

Refractory AML and Progressive Disease

AML is characterized by poor long-term outcomes. Without any anti-AML therapy, the outcomes are further worsened.^{36,37} In a study of 4058 patients with AML, 43% received chemotherapy and 57% received best supportive care only. Nearly 70% of patients treated with chemotherapy died within 1 year of treatment, with a median survival of 7 months, whereas of the patients treated with supportive care only, the median survival was only 1.5 months and 95% died within 1 year. For this study, patient age and Charlson Comorbidity Index score were the primary predictors of whether a patient received chemotherapy.³⁷

Although most patients who undergo induction therapy will initially achieve a CR, the most common cause of death is subsequent relapse of disease. Walter et al found that, after 1 to 2 courses of induction therapy, CR was achieved in 79% of patients with newly diagnosed AML; however, 57% were either primary refractory or had RFS of 12 months or less.³⁸ Treatment options for R/R AML include aggressive therapies, such as high-dose cytarabine (HiDAC)-based therapies (single agent or combinations such as fludarabine/Ara-C/granulocyte colony-stimulating factor/idarubicin [FLAG-Ida], cladribine/idarubicin/Ara-C [CLIA], mitoxantrone/etoposide/Ara-C [MEC], and others) that are aimed at providing a bridge to alloHSCT, considered the only potentially curative option for patients with R/R

AML.³⁹ With HiDAC-based therapies, toxicities such as neutropenic fever, infection, and neurotoxicity are concerns. Furthermore, 1-year and 5-year OS for R/R patients are roughly 29% and 11%, respectively, and as few as one-third of patients may proceed to alloHSCT.^{40,41} Barriers to receiving alloHSCT include procuring suitable donors for patients, maintaining a good performance status, being free of infections, and harboring minimal comorbidities while maintaining a remission.⁴² The remaining alternatives are less-aggressive therapies such as hypomethylating agents or low-dose cytarabine, as well as best supportive care with palliative intent for patients who are not candidates for an aggressive approach.¹⁹

For patients with relapsed AML who are able to proceed to alloHSCT, the outlook remains grim. Bejanyan et al examined a large group of patients with relapsed AML (N = 1788) who had their relapse after alloHSCT. In this group, the median time from transplantation to relapse was 7 months. The majority of patients received treatment for the relapse after alloHSCT, which included chemotherapy, a second HSCT with or without chemotherapy, and/or donor lymphocyte infusion, or donor lymphocyte infusion with or without chemotherapy. Outcomes were poor, with only 15% of patients achieving a subsequent CR. Survival at 1 year after transplant was 23%, and estimated 3-year survival dropped to 8%.⁴³ Nonetheless, alloHSCT remains the only realistic hope for a cure in patients with relapsed AML. Therefore, it is apparent that options for patients who have R/R AML are inadequate.

Economic Burden of AML

AML accounts for approximately 1.1% of new cancer cases each year in the United States.² Despite the relatively low incidence rate of AML compared with other cancers, the economic burden of AML to commercial insurers in the United States is substantial.⁴⁴ For patients with AML, the driving cost component is hospitalization-related costs during induction therapy and alloHSCT-related costs. After induction therapy is complete, costs associated with outpatient care for pharmacy, laboratory monitoring, and doctor’s visits may depend on response to induction therapy.

Although it can be difficult to make direct comparisons among studies because of methodologic differences, treatment approach, and variable costs across centers of care, they all show that AML is costly. According to incidence data in the United States, when combining costs of AML therapies for all treatment episodes (induction therapy, consolidation therapy, supportive treatment during CR, and salvage for relapsed or refractory patients), the estimated total economic burden of AML is approximately \$500 million in patients older than 65 years and \$1.5 billion in patients younger than 65 years.⁴⁵ Notably, the cost of alloHSCT is the highest of all the treatment modalities used for AML and varies across centers of care.

The annual economic burden of AML was explored in a retrospective healthcare claims analysis (2008–2015) in a commercially

insured population of 26,344 patients with AML. Of the claims from 11,170 newly diagnosed patients with AML, total annual average healthcare costs of AML-related inpatient and outpatient costs were \$352,138 per patient per year. Inpatient care was the driver of healthcare costs and represented 70% of annual AML-related costs.⁴⁴ Notably, the younger population had higher healthcare costs; patients aged 45 to 59 years had total costs of \$377,423, compared with patients 60 years and older with \$320,465.⁴⁴

In addition to the expected inpatient care associated with AML, outpatient resource utilization with multiple emergency department (ED) visits and hospitalizations are common in patients with AML. In a single-center retrospective chart review of 52 patients with AML, 75% of patients with AML who underwent induction therapy had at least 1 unplanned ED visit or hospitalization within the first year of treatment. The majority of patients achieved remission (65%) after induction treatment; however, the number of unplanned ED visits were not significantly associated with the patient's remission status at time of discharge from the hospital after induction. Patients younger than 50 years and those with private insurance had a higher number of ED visits. The most common reasons for the unplanned ED visits were neutropenic fever or infection (62%), respiratory events (10%), and anemia or thrombocytopenia (7%).⁴⁶

AlloHSC T Costs

Broder et al examined healthcare costs from the date of alloHSC T to day 100 after alloHSC T, as well as 1-year follow-up after alloHSC T, and found that total median costs were \$289,283 and \$408,876, respectively, with much of the inpatient cost related to the HSC T procedure and the admission for stem cell infusion itself. In this study, alloHSC T patients spent 35.6 days (median) being hospitalized for the HSC T procedure and another 9 days and 26.6 days in the hospital after the procedure, per 100 days after alloHSC T and 1 year after alloHSC T follow-up, respectively).⁴⁷

Induction chemotherapy followed by alloHSC T further drives up the total costs of AML-related healthcare with greater need for hospitalizations. To gain a better understanding of the costs for younger patients with private insurance, healthcare costs and utilization were analyzed using commercial claims from 2007 to 2011 during the first year of treatment after AML diagnosis for privately insured patients aged 50 to 64 years who received either chemotherapy alone or chemotherapy followed by alloHSC T. Relative to chemotherapy only, inpatient and outpatient costs and resource utilization within the first year were substantially higher in patients undergoing chemotherapy followed by alloHSC T. Adjusted healthcare costs for patients undergoing chemotherapy alone averaged \$280,788, compared with \$544,178 for patients receiving chemotherapy followed by alloHSC T.⁴⁸ Within the first year of diagnosis, the majority of AML-related costs for patients treated with chemotherapy only or chemotherapy followed by alloHSC T were from inpatient

care. Patients receiving chemotherapy followed by alloHSC T also required more-frequent outpatient care than patients receiving chemotherapy alone (74.5 vs 49.5 outpatient visits, respectively).⁴⁸

Healthcare Costs per Phase of Treatment

The costs of AML induction were evaluated in different treatment episodes and in respect to duration of treatment for privately insured and Medicare populations with newly diagnosed AML. On average, induction therapy costs were higher for commercially insured patients with AML than for Medicare beneficiaries per treatment episode (\$145,189 vs \$85,734, respectively). The average inpatient costs of consolidation cycles with chemotherapy were less varied between the 2 cohorts; consolidation cycles in commercially insured patients with AML were \$28,137 per treatment episode, compared with \$28,843 per treatment episode for Medicare beneficiaries.⁴⁹

Healthcare resource utilization and direct healthcare costs were investigated across AML treatment phases in an analysis of commercial US healthcare claims from 2008 to 2016. Costs of care from various treatment episodes (starting with the initial induction and ending with initiation of a different AML care episode) or end of follow-up were captured. High-intensity chemotherapy induction with cytarabine with an anthracycline in the inpatient setting within 3 months of diagnosis cost, on average, \$198,582 per cycle, with a mean follow-up of 2.1 months, whereas consolidation cycles (cytarabine with or without an anthracycline use) started within 2 months of induction cost an average of \$73,304 per cycle.⁵⁰ With both induction and consolidation, hospitalization accounted for the largest portion of healthcare costs, at \$178,891 and \$55,301, respectively. Overall, the cost of HSC T was highest, with a mean cost of \$329,621, of which the hospitalization costs accounted for 62% of the overall costs (\$244,801).⁵⁰ R/R disease after treatment with induction chemotherapy or HSC T also poses a substantial economic burden. On average, the cost of relapse was \$145,634; 75% of patients required hospitalization, which accounted for \$101,420 of the average cost.⁵⁰ When compared with patients with CR after induction, those with R/R disease had substantially higher costs. The costs of maintenance of CR consisted primarily of laboratory monitoring and supportive care. R/R disease is far more costly than maintaining CR due to the costs of additional rounds of salvage chemotherapy, additional hospital admissions for salvage chemotherapy, and associated complications and outpatient clinic visits.^{45,50} Therefore, it is undeniable that achieving and maintaining CR is in the best interest of the patient not only clinically, but also financially.

Unmet Patient Needs

Quality of Life and Psychosocial Considerations

Some of the most difficult challenges facing patients with AML and those treating and caring for patients with AML are related to quality

of life (QOL) and psychosocial well-being. Importantly, diminished QOL and psychosocial well-being often appear to be associated with the disease process itself, rather than the treatment of the disease. A study conducted in 33 patients with AML found that symptom burden (especially fatigue, inability to engage in hard work, and feeling anxious), FACT-G scores (a general QOL measurement tool), FACT-Leu scores (a QOL measurement tool specific to leukemia), and DT scores (a measure of psychological distress) worsened with proximity to death.⁵¹ In another study, conducted in 22 patients with AML, 4 QOL-related themes emerged in the analysis: physical symptoms, psychological issues, uncertainty regarding prognosis, and patients' sources of support. Some of the specific challenges noted by patients included feelings of helplessness/hopelessness, caregiver burden/stress, and lack of certainty regarding prognosis and treatment decision-making.⁵² Due to the sudden onset and need to treat rapidly, patients with AML also reported feeling overwhelmed and had trouble processing the large quantity of information regarding their diagnosis and potential treatment options, which may have contributed to increases in psychological distress and feelings of helplessness.⁵³

Several studies have shown the psychological burden of AML on the younger patient population. In a study population in which leukemia was the most prevalent form of cancer, emotion-related concerns of depression and anxiety affected 64% of the young adults.⁵⁴ In another study, conducted in patients aged 18 to 40 with hematologic malignancies, 23% met study-defined criteria for anxiety and 28% met criteria for depression.⁵⁵ This evidence suggests that QOL and psychosocial well-being should be important concerns for caregivers, medical providers, and patients in the AML setting.

Risk of Second Primary Malignancies

Adult patients with AML have a 17% higher risk of developing an SPM than the general population. In a large study (N = 5091), Ghimire et al found that almost 3% of patients with AML developed an SPM within 6 months of their AML diagnosis, where the median time from being diagnosed with AML to development of an SPM was 37.5 months.⁷ The trend for the development of an SPM was 0.5% at completion of 6 months, 25% by 14 months, 50% by 37.5 months, and 75% by 87.5 months.⁷ Although evidence suggests that survival rates are worse in patients who develop AML as an SPM, especially in younger patients, it is not clear whether patients who develop an SPM after being diagnosed with AML experience worse survival rates—however, this observation has been made by others.^{7,56} Leung et al examined SPMs in a small group (N = 5) of very young patients (all younger than 15 years) and found that 3 of the 5 patients were still alive 7 years later, but it is doubtful that this would be the case in older AML patients, who have far worse outcomes relative to children with AML.⁵⁷

TABLE 4. 2017 FDA-Approved Molecular Targeted Therapies for AML⁵⁸⁻⁶¹

Approved Agent	Indication
Enasidenib ⁵⁸	Treatment of adults with relapsed or refractory AML with an <i>IDH2</i> mutation
Midostaurin ⁵⁹	Treatment of adults with newly diagnosed <i>FLT3</i> mutation-positive AML
CPX-351 (daunorubicin and cytarabine) ⁶⁰	Treatment of adults with newly diagnosed therapy-related AML or AML with myelodysplasia-related changes
Gemtuzumab ozogamicin ⁶¹	Treatment of newly diagnosed CD33-positive AML in adults and for treatment of relapsed or refractory CD33-positive AML in adults and in pediatric patients ≥ 2 years

AML indicates acute myeloid leukemia; FLT3, fms-like tyrosine kinase 3; IDH2, isocitrate dehydrogenase 2.

Emerging Treatments

Several promising treatments are emerging in the AML setting. It is hoped that new treatment options will provide better outcomes and relieve the burden of AML on the US healthcare system. Several therapies, including novel cytotoxic formulations, molecular targeted therapies, and immune antibody therapies, have recently gained FDA approval for patients with AML (Table 4).⁵⁸⁻⁶¹ Several additional agents are under investigation for use as single agents or as combination therapy to target a variety of AML subpopulations.⁶²⁻⁶⁵

Conclusions

AML is a heterogeneous disorder characterized by different cytogenetic and molecular profiles, which makes it difficult to treat. Cytogenetic and molecular studies have done much to advance understanding of the underlying mechanisms of this disease, but effective, long-lasting, low-toxicity therapeutic options are still lacking. During induction therapy, current treatments can elicit CR in most patients, but the chance of relapse is high, and long-term outcome is still poor. Once in consolidation, most patients are treated with either intermediate- or high-dose anthracyclines and/or alloHSCT. However, these therapies are not options for all patients with AML because of poor risk-benefit ratios that are influenced by age of the patient, presence of comorbidities, disease status of the patient, cytogenetic/molecular risk stratification, and toxicity. Several unmet needs exist in AML treatment, such as the need for more-effective, less-toxic treatments, reduction of AML-related healthcare costs, and concerns surrounding psychosocial factors, such as QOL. Emerging treatments that make use of growing knowledge of the genetic underpinnings of different AML subtypes seem promising on all fronts. As options for target and immune therapies continue to emerge, large, carefully conducted clinical trials will be vital to improving outcomes in a disease long characterized by poor survival. ■

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REFERENCES

- Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015;136(5):E359-E386. doi: 10.1002/ijc.29210.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7-30. doi: 10.3322/caac.21442.
- Noone A, Howlander N, Krapcho M, et al. SEER cancer statistics review (CSR) 1975-2015. National Cancer Institute website. seer.cancer.gov/csr/1975_2015/. Published April 16, 2018. Accessed July 21, 2018.
- Alibhai SM, Leach M, Minden MD, Brandwein J. Outcomes and quality of care in acute myeloid leukemia over 40 years. *Cancer*. 2009;115(13):2903-2911. doi: 10.1002/cncr.24373.
- Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood*. 2006;107(9):3481-3485. doi: 10.1182/blood-2005-09-3724.
- Buchner T, Berdel WE, Haferlach C, et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: a study by the German Acute Myeloid Leukemia Cooperative Group. *J Clin Oncol*. 2009;27(1):61-69. doi: 10.1200/JCO.2007.15.4245.
- Ghimire KB, Shah BK. Second primary malignancies in adult acute myeloid leukemia—a US population-based study. *Anticancer Res*. 2014;34(7):3855-3859.
- Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood*. 2002;100(13):4325-4336. doi: 10.1182/blood-2002-03-0772.
- Crane MM, Strom SS, Halabi S, et al. Correlation between selected environmental exposures and karyotype in acute myelocytic leukemia. *Cancer Epidemiol Biomarkers Prev*. 1996;5(8):639-644.
- Kayser S, Döhner K, Krauter J, et al; German-Austrian AMLSG. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. *Blood*. 2011;117(7):2137-2145. doi: 10.1182/blood-2010-08-301713.
- Sanderson RN, Johnson PR, Moorman AV, et al. Population-based demographic study of karyotypes in 1709 patients with adult acute myeloid leukemia. *Leukemia*. 2006;20(3):444-450. doi: 10.1038/sj.leu.2404055.
- Grimwade D, Ivey A, Huntly BJ. Molecular landscape of acute myeloid leukemia in younger adults and its clinical relevance. *Blood*. 2016;127(1):29-41. doi: 10.1182/blood-2015-07-604496.
- Grimwade D, Hills RK, Moorman AV, et al; National Cancer Research Institute Adult Leukaemia Working Group. Refinement of cytogenetic classification in acute myeloid leukemia: determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom Medical Research Council trials. *Blood*. 2010;116(3):354-365. doi: 10.1182/blood-2009-11-254441.
- Mrózek K, Marcucci G, Nicolet D, et al. Prognostic significance of the European LeukemiaNet standardized system for reporting cytogenetic and molecular alterations in adults with acute myeloid leukemia. *J Clin Oncol*. 2012;30(36):4515-4523. doi: 10.1200/JCO.2012.43.4738.
- Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424-447. doi: 10.1182/blood-2016-08-733196.
- Wang ML, Bailey NG. Acute myeloid leukemia genetics: risk stratification and implications for therapy. *Arch Pathol Lab Med*. 2015;139(10):1215-1223. doi: 10.5858/arpa.2015-0203-RA.
- Huang BT, Wang Y, Du QF, et al. Analysis of efficacy and cost-effectiveness of high-dose arabinoside versus daunorubicin chemotherapy in older adult patients with acute myeloid leukemia by cytogenetic risk profile: retrospective review from China. *Int J Hematol*. 2011;93(4):474-481. doi: 10.1007/s12185-011-0804-0.
- Ley TJ, Miller C, Ding L, et al; Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368(22):2059-2074. doi: 10.1056/NEJMoa1301689.
- Fey MF, Buske C, ESMO Guidelines Working Group. Acute myeloblastic leukaemias in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013(24 suppl 6):vi138-vi143. doi: 10.1093/annonc/mdt320.
- Melnick AM, Levine RL, Figueroa ME, Thompson CB, Abdel-Wahab O. Epigenetic effects of IDH1/IDH2 mutations. *Blood*. 2011;118(21):SC1-SC33.
- Ohtake S, Miyawaki S, Fujita H, et al. Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. *Blood*. 2011;117(8):2358-2365. doi: 10.1182/blood-2010-03-273243.
- Yates J, Glidewell O, Wiernik P, et al. Cytosine arabinoside with daunorubicin or adriamycin for therapy of acute myelocytic leukemia: a CALGB study. *Blood*. 1982;60(2):454-462.
- Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1249-1259. doi: 10.1056/NEJMoa0904544.
- Löwenberg B, Ossenkoppele GJ, van Putten W, et al; Dutch-Belgian Cooperative Trial Group for Hemato-Oncology (HOVON); German AML Study Group (AMLSG); Swiss Group for Clinical Cancer Research (SAKK) Collaborative Group. High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med*. 2009;361(13):1235-1248. doi: 10.1056/NEJMoa0901409.
- Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. *J Clin Oncol*. 2010;28(5):808-814. doi: 10.1200/JCO.2009.23.2652.
- Röllig C, Müller-Tidow C, Hüttmann A, et al. Sorafenib versus placebo in addition to standard therapy in younger patients with newly diagnosed acute myeloid leukemia: results from 267 patients treated in the randomized placebo-controlled SAL-Soramil trial. *Blood*. 2014;124(21):6.
- Serve H, Krug U, Wagner R, et al. Sorafenib in combination with intensive chemotherapy in elderly patients with acute myeloid leukemia: results from a randomized, placebo-controlled trial. *J Clin Oncol*. 2013;31(25):3110-3118. doi: 10.1200/JCO.2012.46.4990.
- Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 trial. *J Clin Oncol*. 2011;29(4):369-377. doi: 10.1200/JCO.2010.31.4310.
- Hills RK, Castaigne S, Appelbaum FR, 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):986-996. doi: 10.1016/S1470-2045(14)70281-5.
- Burnett AK, Russell NH, Hills RK, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukemia. *J Clin Oncol*. 2012;30(32):3924-3931. doi: 10.1200/JCO.2012.42.2964.
- Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet*. 2012;379(9825):1508-1516. doi: 10.1016/S0140-6736(12)60485-1.
- Taksin AL, Legrand O, Raffoux E, 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*. 2006;21(1):66-71. doi: 10.1038/sj.leu.2404434.
- Yanada M, Matsuo K, Emi N, Naoe T. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. *Cancer*. 2005;103(8):1652-1658. doi: 10.1002/cncr.20945.
- Schäch M, Röllig C, Soucek S, et al. Cytarabine dose of 36 g/m² compared with 12 g/m² within first consolidation in acute myeloid leukemia: results of patients enrolled onto the prospective randomized AML96 study. *J Clin Oncol*. 2011;29(19):2696-2702. doi: 10.1200/JCO.2010.33.7303.
- Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and Leukemia Group B. *N Engl J Med*. 1994;331(14):896-903. doi: 10.1056/NEJM199410063311402.
- Bories P, Bertoli S, Berard E, et al. Intensive chemotherapy, azacitidine, or supportive care in older acute myeloid leukemia patients: an analysis from a regional healthcare network. *Am J Hematol*. 2014;89(12):E244-E252. doi: 10.1002/ajh.23848.
- Meyers J, Yu Y, Kaye JA, Davis KL. Medicare fee-for-service enrollees with primary acute myeloid leukemia: an analysis of treatment patterns, survival, and healthcare resource utilization and costs. *Appl Health Econ Health Policy*. 2013;11(3):275-286. doi: 10.1007/s40258-013-0032-2.
- Walter RB, Othman M, Burnett AK, et al. Resistance prediction in AML: analysis of 4601 patients from MRC/NCRI, HOVON/SAKK, SWOG and MD Anderson Cancer Center. *Leukemia*. 2015;29(2):312-320. doi: 10.1038/leu.2014.242.
- Ramos NR, Mo CC, Karp JE, Hourigan CS. Current approaches in the treatment of relapsed and refractory acute myeloid leukemia. *J Clin Med*. 2015;4(4):665-695. doi: 10.3390/jcm4040665.
- Breems DA, Van Putten WL, Huijgens PC, et al. Prognostic index for adult patients with acute myeloid leukemia in first relapse. *J Clin Oncol*. 2005;23(9):1969-1978. doi: 10.1200/JCO.2005.06.027.
- Veltri LW, Anders B, Kanate AS, Shillingburg A, Craig MD, Cumpston A. Outcomes of six-dose high-dose cytarabine (HIDAC-6) as a salvage regimen for patients with relapsed/refractory acute myeloid leukemia (RR-AML). *J Clin Oncol*. 2016;34(15)(suppl):e18508-e18508.
- Deeg HJ, Sandmaier BM. Who is fit for allogeneic transplantation? *Blood*. 2010;116(23):4762-4770. doi: 10.1182/blood-2010-07-259358.
- Bejanyan N, Weisdorf DJ, Logan BR, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. *Biol Blood Marrow Transplant*. 2015;21(3):454-459. doi: 10.1016/j.bbmt.2014.11.007.
- Hagiwara M, Sharma A, Chung KC, Delea TE. Burden of acute myeloid leukemia (AML) in a U.S. commercially insured population. *J Clin Oncol*. 2017;35(15)(suppl):e18330-e18330.
- Mahmoud D, Skikne BS, Kucmin-Bemelms I, Alteman C, Hensen M. Overall economic burden of total treatment costs in acute myeloid leukemia throughout the course of the disease. *Blood*. 2012;120(21):3614-3614.
- Bryant AL, Deal AM, Walton A, Wood WA, Muss H, Mayer DK. Use of ED and hospital services for patients with acute leukemia after induction therapy: one year follow-up. *Leuk Res*. 2015;39(4):406-410. doi: 10.1016/j.leukres.2015.01.006.
- Broder MS, Quock TP, Chang E, et al. The cost of hematopoietic stem-cell transplantation in the United States. *Am Health Drug Benefits*. 2017;10(7):366-374.
- Preussler JM, Meyer CL, Mau LW, 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):1021-1028. doi: 10.1016/j.bbmt.2017.02.017.

49. Stein EM, Bonifacio G, Latremouille-Viau D, et al. Treatment patterns, healthcare resource utilization, and costs in patients with acute myeloid leukemia in commercially insured and Medicare populations. *J Med Econ.* 2018;21(6):556-563. doi: 10.1080/13696998.2018.1425209.
50. Medeiros BC, Pandya BJ, Chen CC, et al. Economic burden of treatment episodes in acute myeloid leukemia (AML) patients in the US: a retrospective analysis of a commercial payer database [abstract]. *Blood.* 2017;130(suppl 1):4694.
51. Lowe JR, Yu Y, Wolf S, Samsa G, LeBlanc TW. A cohort study of patient-reported outcomes and healthcare utilization in acute myeloid leukemia patients receiving active cancer therapy in the last six months of life. *J Palliat Med.* 2018;21(5):592-597. doi: 10.1089/jpm.2017.0463.
52. Boucher NA, Johnson KS, LeBlanc TW. Acute leukemia patients' needs: qualitative findings and opportunities for early palliative care. *J Pain Symptom Manage.* 2018;55(2):433-439. doi: 10.1016/j.jpainsymman.2017.09.014.
53. LeBlanc TW, Fish LJ, Bloom CT, et al. Patient experiences of acute myeloid leukemia: a qualitative study about diagnosis, illness understanding, and treatment decision-making. *Psychooncology.* 2017;26(12):2063-2068. doi: 10.1002/pon.4309.
54. Sodergren SC, Husson O, Rohde GE, et al. A life put on pause: an exploration of the health-related quality of life issues relevant to adolescents and young adults with cancer [published online March 22, 2018]. *J Adolesc Young Adult Oncol.* 2018. doi: 10.1089/jayao.2017.0110.
55. Muffly LS, Hlubocky EJ, Khan N, et al. Psychological morbidities in adolescent and young adult blood cancer patients during curative-intent therapy and early survivorship. *Cancer.* 2016;122(6):954-961. doi: 10.1002/cncr.29868.
56. Keegan THM, Bleyer A, Rosenberg AS, Li Q, Goldfarb M. Second primary malignant neoplasms and survival in adolescent and young adult cancer survivors. *JAMA Oncol.* 2017;3(11):1554-1557. doi: 10.1001/jamaoncol.2017.0465.
57. Leung W, Ribeiro RC, Hudson M, et al. Second malignancy after treatment of childhood acute myeloid leukemia. *Leukemia.* 2001;15(1):41-45.
58. Idhifa [prescribing information]. Summit, NJ: Celgene Corporation; 2017.
59. Rydapt [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017.
60. Vyxeos [prescribing information]. Dublin, Republic of Ireland: Jazz Pharmaceuticals, Inc.; 2017.
61. Mylotarg [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals Inc.; 2018.
62. Popovici-Muller J, Lemieux RM, Artin E, et al. Discovery of AG-120 (Ivosidenib): A first-in-class mutant IDH1 inhibitor for the treatment of IDH1 mutant cancers. *ACS Med. Chem. Lett.* 2018;9(4):300-305. doi: 10.1021/acsmchemlett.7b00421.
63. DiNardo CD, Rausch CR, Benton C, et al. Clinical experience with the BCL2-inhibitor venetoclax in combination therapy for relapsed and refractory acute myeloid leukemia and related myeloid malignancies. *Am J Hematol.* 2018;93(3):401-407. doi: 10.1002/ajh.25000.
64. Galanis A, Ma H, Rajkhowa T, et al. Crenolanib is a potent inhibitor of FLT3 with activity against resistance-conferring point mutants. *Blood.* 2014;123(1):94-100. doi:10.1182/blood-2013-10-529313.
65. Lee LY, Hernandez D, Rajkhowa T, et al. Preclinical studies of gilteritinib, a next-generation FLT3 inhibitor. *Blood.* 2017;129(2):257-260. doi:10.1182/blood-2016-10-745133.