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New and Emerging Therapies for Acute Myeloid Leukemia

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Abstract

The treatment of acute myeloid leukemia (AML) has remained relatively unchanged for the past three to four decades with generally poor outcomes, especially in elderly populations unfit for intensive therapy. Recent advancements, however, have identified several cytogenetic and molecular markers that have not only improved prognostication, but have also led to the development of several new targeted therapies for specific subpopulations. In 2017, the U.S. Food and Drug Administration (FDA) approved four new treatments with indications for FLT3-mutated AML (midostaurin), newly diagnosed or relapsed/refractory CD33+ AML (gemtuzumab ozogamicin), newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (CPX-351), and relapsed/refractory AML with an IDH2 mutation (enasidenib). These newly approved therapies have demonstrated improved response in their target populations in several pivotal clinical trials with some also demonstrating improved overall survival. Additional novel therapies in development for AML include agents that target BCL2, FLT3, IDH1, the ubiquitination pathway, as well as cell therapy using engineered T-cells with chimeric antigen receptors (CAR-T cells). This review provides a summary of the four newly approved therapies for AML, as well as several promising therapies currently in development.

Keywords

Acute Myeloid Leukemia; Molecular; Targeted; Therapy

INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous malignant disorder of the myeloid lineage characterized by uncontrolled clonal proliferation of immature cells [1]. Although AML may be found on routine blood cell count testing, definitive diagnosis routinely involves bone marrow biopsy with morphologic, immunohistochemical, flow cytometric, cytogenetic and molecular analyses. Per the 2016 World Health Organization (WHO) update on myeloid disorders, AML is diagnosed by 20% or greater myeloblasts in the peripheral blood or bone marrow [2]. The WHO system classifies AML into several subtypes, including AML with recurrent genetic abnormalities, AML with myelodysplasia-related changes, therapy-related myeloid neoplasms, and AML not otherwise specified. The incidence of AML ranges between 3 to 8 cases per 100,000 adults yearly, with 9 to 17 cases per 100,000 adults aged 65 or greater [3]. Several risk factors for the development of AML have been identified, including antecedent hematologic malignancies, chemotherapy and radiation exposure, and certain congenital disorders [4]. Median age of diagnosis ranges between 67 to 70 years of age. Median overall survival (OS) at 5 years for patients younger than 60 years is approximately 40%, compared to approximately 10% for patients greater than 60 years [1]. In older patients who are unable to undergo leukemia-specific therapy, survival typically ranges from around 4 months with best supportive care to approximately 10 months with lower-intensity therapies such as azacitidine, a hypomethylating agent [5].

Although the molecular heterogeneity of AML has become better appreciated over the past decade, the standard treatment for AML had not changed for the past three to four decades until multiple new drug approvals in 2017. Treatment for AML includes remission induction chemotherapy and post-remission consolidation therapy including chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT). In eligible adults with newly diagnosed AML, the traditional standard therapy is "7+3" induction chemotherapy with infusional cytarabine for 7 days with 3 days of anthracycline chemotherapy (daunorubicin or idarubicin) [6]. A complete remission (CR) is achieved in 60 to 85% of patients younger than the age of 60, and in 40 to 60% of patients greater than the age of 60 [7]. Patients with a favorable genetic risk profile typically undergo additional consolidation chemotherapy, whereas those with intermediate-risk AML undergo either chemotherapy or allo-HSCT and those with unfavorable-risk AML are recommended for allo-HSCT [8]

Several genetic lesions and morphologic features have been identified as prognostic markers with clinical significance, and importantly, some carry predictive/actionable value (Table 1). During initial diagnostic workup, European LeukemiaNet (ELN) recommends screening for mutations in *NPM1, CEBPA, RUNX1, ASXL1* and *FLT3* at diagnosis [8]. Mutations in isocitrate dehydrogenase 2 (*IDH2*) are also often tested for initially, due to their newly actionable status in the relapsed or refractory (R/R) setting. Mutations in *NPM1* are found in 25 to 35% of patients with AML, most frequently associated with normal karyotype [1]. Isolated mutations in *NPM1* are associated with favorable prognosis [9], and in this population NPM1 has been used as a pilot genetic marker for assessing minimal residual disease after induction [10]. Bi-allelic mutations in *CEBPA* are associated with a favorable outcome, as well as with familial AML, and are found in 6 to 10% of patients. FLT3-internal tandem duplication (FLT3-ITD) mutations are found in approximately 20% of patients with

AML, most often associated with normal cytogenetics, and are associated with an unfavorable outcome in some patients [11]. Patients with a mutation in FLT3-ITD may benefit from allo-HSCT in first CR as well as from tyrosine kinase inhibitors (TKIs) that have either been approved or are in clinical trials. Despite the rapid development of prognostic and predictive molecular characteristics, history and morphologic, immunophenotypic and cytogenetic evaluation at diagnosis remain crucial as there are newly-approved frontline agents shown to have OS benefit with myelodysplasia-related changes or therapy-related AML and AML expressing CD33. This article aims to review the four recently approved AML therapies as well as some in advanced development, as the landscape of AML therapy has changed more in the last year than in many decades prior.

NEWLY-APPROVED THERAPIES FOR AML

Midostaurin

Midostaurin (Rydapt, Novartis Pharmaceuticals, Inc.) is a multi-targeted kinase inhibitor that was the first of four novel therapies to receive FDA approval for treatment of AML in 2017. As discussed, FLT3 mutations are found in approximately 20-30% of patients with newly diagnosed AML, and are associated with a poor outcome. Most FLT3 mutations are of the internal tandem duplication mutation (ITD) subtype, which is associated with a high relapse rate when there is high mutant to wild-type *FLT3* allelic ratio. A smaller subset of FLT3 mutations are of the tyrosine kinase domain (TKD) subtype. Midostaurin was evaluated in a large, international phase III study, the CALGB 10603/RATIFY trial (Table 2). In this randomized, double-blinded, placebo-controlled study, patients younger than age 60 with newly diagnosed FLT3-mutated (both ITD and TKD) AML were randomized to standard 7+3 chemotherapy with either midostaurin or placebo [20]. Patients who achieved CR following induction therapy received four cycles of consolidation therapy with high-dose cytarabine (HiDAC) and midostaurin/placebo maintenance for up to 1 year. Allo-HSCT was performed in 25% of patients who achieved first CR, although this was not mandated by study protocol. The study demonstrated that combination 7+3 chemotherapy and midostaurin led to a significant improvement in overall survival, with a median OS of 74.7 months in the midostaurin group versus 25.6 months (hazard ratio for death 0.78, p=0.009) with placebo. Subgroup analysis between the low allelic ratio ITD, high allelic ratio ITD, and TKD groups did not show any significant difference in OS. The rate of serious adverse effects (AEs) was not significantly different between the two treatment arms, with the exception of a higher rate of grade 3 or greater rash/desquamation and nausea in the midostaurin arm. The most common AEs associated with midostaurin include nausea, vomiting, headache, fever, and febrile neutropenia. As patients in this study were exposed to midostaurin for induction, consolidation and maintenance, the specific benefit and optimal duration of midostaurin maintenance is unclear.

Gemtuzumab ozogamicin (GO)

Gemtuzumab ozogamicin (Mylotarg ; Pfizer, Inc.) is a humanized immunoglobulin antibody directed against CD33 and conjugated with calicheamicin, a cytotoxic antibiotic. CD33 is a transmembrane receptor that is highly expressed on blasts of most patients with AML. GO promotes single- and double-strand breaks in DNA, ultimately leading to cell death. GO

initially received accelerated FDA approval for CD33+ AML in 2000 based on CR rates in nonrandomized phase II studies. However, a follow-up phase III study [21] in patients with untreated AML comparing standard 7+3 induction chemotherapy plus GO versus 7+3 alone found a higher mortality rate in the GO arm (5.5% versus 1.4%), without any improvement in CR. This led to the withdrawal of GO from the market in 2010. Subsequent trials, however, showed improved OS rates without increased mortality rates [22, 23]. The phase III randomized ALFA-0701 study investigated low fractionated-dose GO with standard first-line chemotherapy in patients with *de novo* AML [24], and found an improvement in median OS in the GO arm (34 months versus 19.2 months, p = 0.046). In subgroup analysis, this benefit was limited to patients with favorable-risk and intermediate-risk karyotypes. Subsequent meta-analysis found that among 3,325 patients in five randomized controlled trials, the addition of GO reduced the risk of relapse and improved OS at five years (34.6% versus 30.7%) [25]. Additionally, at six years, survival benefit was significant in patients with favorable-risk (76.3% versus 55.2%) and intermediate-risk (39.4% versus 34.1%) cytogenetics. These studies including the meta-analysis led to reapplication for FDA approval (at the lower, fractionated dosing), which was granted in September 2017 for patients with newly diagnosed CD33+ AML and also for R/R CD33+ AML, based on the MyloFrance-1 study [26] (Table 2). The most common AEs include nausea, vomiting, transaminitis (elevations in AST or ALT), and hemorrhage. Although GO still retains its black box warning for veno-occlusive disease, events using current approved dosing were rare (2%), and can be associated with prior alkylator chemotherapy.

CPX-351 (Liposomal daunorubicin and cytarabine)

CPX-351 (Vyxeos ; Jazz Pharmaceuticals) is a liposomal formulation of cytarabine and daunorubicin (the standard agents in 7+3 induction chemotherapy) in a fixed, synergistic 5:1 molar ratio. Prior pre-clinical studies had demonstrated that molar ratios of cytarabine and daunorubicin between 1:1 and 10:1 were synergistic, whereas lower ratios were antagonistic [27]. Although CPX-351 is not a targeted therapy, the fixed 5:1 molar ratio and liposomal packaging demonstrated more effective delivery and cytotoxicity to AML blasts. A multicenter, randomized phase II trial compared CPX-351 with investigator's choice of chemotherapy for patients with AML in first relapse [28]. The study demonstrated an improvement in the rate of CR or CR with incomplete hematologic recovery (CRi) in the CPX-351 arm (49.4% versus 40.9%) as well as improvement in median OS in the CPX-351 arm (8.5 months versus 6.3 months). A randomized phase II trial in 2014 comparing CPX-351 to 7+3 chemotherapy in first-line treatment of AML in older patients did not demonstrate a statistically significant difference in OS between the study's two arms; however, response rate was improved (57.6% versus 31.6%, p = 0.06) in patients with secondary AML [29]. This latter phase II trial led to a phase III trial comparing CPX-351 versus 7+3 chemotherapy in patients 60-75 years of age with high-risk secondary AML (untreated therapy-related AML, antecedent myelodysplastic syndrome or CMML, or AML with myelodysplasia-related changes), and confirmed superior OS (9.56 months versus 5.95 months, p = 0.005) in the CPX-351 arm, as well as CR/CRi rates (47.7% versus 33.3%, p = 0.016) [30]. Severe AEs were similar in both treatment arms. CPX-351 subsequently received FDA approval through Priority Review and Breakthrough Therapy designations for

newly diagnosed therapy-related AML or AML with myelodysplasia-related changes in August 2017 (Table 2).

Enasidenib

Enasidenib (Idhifa, Agios Pharmaceuticals, Inc. and Celgene Corporation) is a selective inhibitor of mutated IDH2. Mutations in *IDH2* occur in approximately 10% of patients with AML [4], and lead to the synthesis of 2-hydroxyglutarate, which results in DNA and histone hypermethylation and impaired cellular differentiation. Enasidenib received FDA approval in August 2017 for IDH2-mutant R/R AML at a dosing of 100 mg orally once per day (Table 2). In the first-in-human phase I/II study published in 2017, enasidenib at the approved dose produced CR/(CRi) in 26.6% of patients with R/R AML [31]. An additional 12% of patients experienced either a partial response (PR) or achieved a morphologic leukemia-free state (where blasts are not increased but no recovery of any cell lineage has occurred), corresponding to an overall response rate (ORR) of 38.5%. Median time to best response was 3.7 months. Median OS was 9.3 months (95% CI 8.2 to 10.9 months) overall, with a median OS of 19.7 months in patients who achieved CR. Of note, individuals with clinical responses did not have a reduction in *IDH2* mutant allele burden, reflecting a shift from undifferentiated to differentiated clonal hematopoiesis. The most common AEs from enasidenib included nausea and indirect hyperbilirubinemia. Hyperleukocytosis secondary to *en masse* differentiation was also seen infrequently (<4%), and was managed with hydroxyurea. The most distinct AE was IDH-inhibitor-associated differentiation syndrome (IDH-DS), which occurred in approximately 10% of patients in this study. IDH-DS typically occurred within 3-4 months of treatment initiation, and did not have a pathognomonic sign or symptom. IDH-DS typically presented with new or worsening dyspnea or hypoxemia, new or worsening pulmonary infiltrates on radiographs, new or worsening peripheral edema, and worsening renal function [32]. As there is no available confirmatory laboratory testing for IDH-DS, careful clinical evaluation for suspected IDH-HS is warranted. Based off the study authors' experience, recommended treatment for IDH-DS is corticosteroids (e.g. dexamethasone 10 mg every 12 hours) started immediately, and to briefly hold enasidenib until there is improvement in symptoms.

THERAPEUTICS IN DEVELOPMENT FOR AML

Several novel anti-AML agents are in various stages of development. Examples are highlighted in Table 3 and described in the following sections.

Venetoclax

Venetoclax is an oral targeted small molecule that inhibits BCL2, an important anti-apoptotic protein expressed in AML [33]. Venetoclax was approved in April 2016 for use in chronic lymphocytic lymphoma (CLL) with a 17p deletion after one prior therapy, and is undergoing clinical trial evaluation in many other hematologic neoplasms, including AML. Initial activity was modest (ORR 19%) as monotherapy in a nonrandomized phase II trial in R/R AML [34], but a subsequent nonrandomized phase II study combining venetoclax with hypomethylating agents azacitidine or decitabine in the upfront elderly population unfit for intensive chemotherapy showed an ORR of 67%. Primary AEs were cytopenias, as is seen in

CLL. Only 5 of 145 patients died within 1 month of starting drug [35]. Based on these results and other phase II trials [36, 37], two phase III randomized clinical trials are under way in adults with AML ineligible for standard induction chemotherapy, one () evaluating venetoclax with azacitidine versus azacitidine alone, the other () studying venetoclax with low-dose cytarabine (LDAC) vs LDAC alone. These combinations may offer this population much more efficacious options, considering traditionally poor overall outcomes.

FLT3 Inhibitors

In addition to midostaurin, other FLT3 inhibitors are undergoing evaluation for use in AML. Sorafenib is a multi-kinase inhibitor currently approved for use in advanced hepatocellular carcinoma, renal cell carcinoma, and differentiated thyroid cancer. Preclinical data and earlyphase clinical trials suggested some activity in AML, which led to the German SORAML randomized phase II trial [38]. In 267 patients with previously untreated AML, the study compared the addition of sorafenib versus placebo to standard induction and consolidation chemotherapy and then sorafenib or placebo to 12 months of maintenance. Patients were not tested or selected for FLT3 mutations as part of the study protocol. Median event-free survival (EFS) was prolonged with sorafenib compared to placebo (21 months vs 9 months), with a significantly longer 3-year EFS (40% vs 22%, HR 0.64, p = 0.013), although adverse events of fever, diarrhea, bleeding, cardiac events, and hand-foot-skin reactions were increased. Nonrandomized data also suggests improved outcomes compared to historical controls with sorafenib added to induction and consolidation chemotherapy in those with FLT3-ITD and FLT3-TKD mutations [39] and in the relapsed setting after allo-HSCT [40].

Quizartinib is a more selective and potent TKI that inhibits FLT3-wild type and FLT3-ITD activity, but not FLT3-TKD [41]. An open-label phase II trial evaluated quizartinib monotherapy in two cohorts of patients with FTL3-ITD positive or negative R/R AML after second-line chemotherapy or allo-HSCT [42, 43]. The majority of the patients in both cohorts were FLT3-ITD positive. The two cohorts demonstrated promising efficacy of single-agent quizartinib with a composite CR rate (CRc, defined as the combination of CR, CR with incomplete platelet recovery and CRi) of 44-50% in R/R FLT3-ITD positive AML. Common AEs of quizartinib include myelosupression, QT prolongation, nausea, and diarrhea. Two phase III trials are currently investigating quizartinib, QuANTUM-First () which compares standard induction chemotherapy in addition to quizartinib or placebo in newly-diagnosed FTL3-ITD AML patients, and QuANTUM-R (), studying single-agent quizartinib versus salvage chemotherapy in R/R FTL3-ITD positive AML.

Gilteritinib, an inhibitor of both FLT3 and related kinase AXL, has shown promising response data in early phase trials and is now being studied in four phase III trials. In the first-in-human phase I/II study, 252 patients with R/R AML were enrolled, 25% had received prior TKI and 63% had FLT3 mutations. Diarrhea (16%) and fatigue (15%) were the most common treatment-related AEs. ORR was 12% in FLT3-wild-type patients, but was 52% in FLT3-mutated patients receiving   80 mg. This enriched group had a median OS of 31 weeks and median duration of response of 20 weeks [44]. Current phase III trials include the ADMIRAL study () in FLT3-mutated R/R AML compared to salvage chemotherapy.

Gilteritinib is also being evaluated in the maintenance setting for FLT3-ITD-mutated patients after allo-HSCT compared to placebo (), and also in those patients not proceeding with transplant (). In addition, it is being studied in newly diagnosed patients with a FLT3 mutation not eligible for intensive induction chemotherapy in a three-arm study, comparing azacitidine alone, gilteritinib alone, and combination azacitidine and gilteritinib ().

Crenolanib is another second-generation FLT3 inhibitor which has activity in preclinical studies including against resistance mutations that develop with other FLT3 inhibitor therapy [45]. In a single-center open-label phase II study of R/R AML patients with either FLT3-ITD or FLT3-TKD mutations, crenolanib was studied as a single agent. Out of 34 evaluable patients, 13 were FLT3 TKI-naïve, and 21 had progressed on prior FLT3-TKI, and 10 had progressed after Allo-SCT. ORR was 47%, with 23% of the TKI-naïve cohort achieving CRi (5% in the prior TKI cohort). The primary toxicities were abdominal pain and nausea, with no deaths attributed to therapy [46]. Preliminary data from a phase II trial () evaluating crenolanib with 7+3 induction and consolidation in newly-diagnosed FLT3-mutated patients, similar to midostaurin's approved indication, was presented at the ASH 2017 annual meeting. Out of 29 patients, 21 (72%) achieved CR after one induction cycle, three more achieved CR with second induction, high-dose cytarabine, and allo-HSCT. At a median followup of 14 months, one patient out of the 24 achieving CR died of post-transplant complications, and only two relapsed [47]. Crenolanib is now being studied in two randomized phase III studies, one comparing directly to midostaurin in the newly diagnosed setting with induction chemotherapy (), and the other in the R/R setting combined with salvage chemotherapy ().

Ivosidenib (AG120)

Isocitrate dehydrogenase 1 (IDH1) is mutated in approximately 9-16% of AML patients who are most often cytogenetically normal. IDH1 mutations have thus far found to be mutually exclusive with IDH2 mutations [48, 49]. Ivosidenib (AG120, Agios Pharmaceuticals) is a novel IDH1 inhibitor in development, and has been studied in a phase I trial presented at the 2017 ASH annual meeting [50]. In this first-in-human safety study in mutant IDH1 advanced hematologic malignancies including R/R AML, 258 patients received ivosidenib including dose escalation (78 patients) and dose expansion (180 patients) phases. The highest frequency AEs were diarrhea (33%), leukocytosis (30%), nausea (30%), fatigue (29%), febrile neutropenia (25%), dyspnea (24%), anemia (23%), and QT prolongation (23%), most of these being low grade and unrelated to therapy. Differentiation syndrome (DS), as seen with IDH2 inhibitor enasidenib, was seen in 29 patients (11.2%), but no deaths occurred due to DS. Regarding efficacy, ORR was 41.6%, including 21.6% achieving CR and 8.8% with CR with partial hematologic recovery (CRh). Median duration of CR+CRh was 8.2 months. Ivosidenib is currently being studied in a global randomized phase III trial () in untreated IDH1-mutated AML combined with azacitidine or placebo.

Pevonedistat (MLN4924)

Further understanding of AML biology has revealed defects in the ubiquitination/protein degradation system including a process called neddylation, essential for some ubiquitin ligases and subsequent degradation of their substrates [51, 52]. Pevonidostat is a first-in-

class inhibitor of the NEDD8-activating enzyme that works by causing accumulation of otherwise-degraded proteins with antiproliferative effects [17]. After preclinical experiments demonstrated increased reactive oxygen species and apoptosis in AML cell lines and animal models when combined with azacitidine [53, 54], pevonidostat was studied in phase I clinical trials, first in a monotherapy safety study which observed a few CR and PR in a heavily pretreated population [55], and then in a phase Ib study in combination with azacitidine in older AML patients who had not received cytotoxic chemotherapy [56]. Here, dose-limiting toxicities were elevated bilirubin and transaminases, but were reversible without clinical sequelae. The ORR in combination with azacitidine was 60% with a CR/CRi rate of 47% that was not influenced by disease status (*de novo* versus secondary), blast count or cytogenetic risk. After a median follow-up of 16.4 months, median OS was seven months and 12-month survival was 45%. Based on these results, a randomized phase III study of pevonedistat and azacitidine versus azacitidine for patients with treatment naïve higher risk MDS, chronic myelomonocytic leukemia and low blast count AML (up to 30% blasts) is ongoing ().

Adoptive Cell Therapy

Novel cell therapies using engineered T-cells with chimeric antigen receptors (CAR-T cells) are now approved for B-cell acute lymphoblastic lymphoma and R/R large B-cell lymphoma. In AML, preclinical studies have used targets such as CD33 and CD123 with efficacy *in vitro* [57, 58], but the heterogeneous nature of AML makes specificity and on-target, off-tumor effects an issue *in vivo.* Wang, et al. reported treatment of a single patient with refractory AML with CD33-directed CAR-T cell therapy, without any conditioning chemotherapy [59]. Within two weeks, the patient's bone marrow blast percentage decreased from >50% before infusion to <6%. AEs included cytokine-release syndrome (CRS) and worsened cytopenias. Etanercept, an anti-TNF-alpha agent, was administered for anti-inflammatory effects. Unfortunately, despite initial clinical response, blast percentage rose to 70% at 9 weeks with retention of CD33 expression, suggesting an escape mechanism other than CAR target loss. Two phase I studies in China in R/R AML are currently ongoing, with the first studying autologous CD33-directed CAR-Ts (), and the second study using allogeneic CAR-T therapy ().CD123 is another promising target in AML, as it is expressed on AML blasts and leukemic stem cells, but minimally on hematopoietic stem cells [18]. Several other phase I CAR-T trials are currently accruing patients using CD123, CD123/CD28 or CD123/CD33 combinations, among other targets. Overall, major challenges remain regarding elucidation of the best targets or combinations of, CRS, and co-stimulatory molecules that improve efficacy while balancing toxic off-tumor effects. The ideal preparative regimens are also yet to be defined.

Flotetuzumab

Flotetuzumab is a dual-affinity re-targeting antibody (DART), which engages both CD123-expressing AML cells and T-cells via CD3. The dual-targeting antibody-based approach is similar in principle to bispecific T-cell engagers such as blinatumomab, which is currently approved for B-ALL. Preliminary data from a phase I study using flotetuzumab in R/R AML and high-risk MDS was reported at ASH 2017 [60]. Forty-five patients were enrolled, of which 89% had AML. A lower lead-in dose of flotetuzumab was given for the first week to

help mitigate CRS. Drug-related grade 3 or worse AEs were experienced in 44% of patients, the most common toxicity being CRS/infusion-related reaction in 76% of all patients (any grade). Fourteen patients were treated with the maximum tolerated dose and schedule or greater and completed at least one cycle. Six of these (43%) had an objective response (3 CR, 1 CRi, 1 MLFS, 1 PR), two more had stable disease, and correlative studies showed an increase in T-cell activating cytokine levels and CD8-positive T-cells in the bone marrow.

CONCLUSIONS

In summary, 2017 has been a pivotal year for AML clinicians, researchers, and patients. As understanding of AML biology improves, particularly its molecular underpinnings, novel prognostic and targetable subpopulations are being defined (Figure 1). The four newly-approved therapies have changed the standard of care for their respective populations. For those newly diagnosed, fit for intensive therapy and with favorable and intermediate-risk cytogenetic and molecular features, the addition of gemtuzumab ozogomicin improves overall survival when added to 7+3 chemotherapy. For fit patients with a FLT3 mutation, midostaurin significantly improves median OS when added to induction chemotherapy. In newly diagnosed, fit older patients with secondary AML or therapy-related AML, liposomal daunorubicin and cytarabine improves OS and response rate compared to 7+3 with similar rates of AEs. For younger/fit patients without the above features, traditional 7+3 remains the standard upfront therapy. For newly diagnosed unfit patients not eligible for intensive chemotherapy, hypomethylating agents remain the standard of care, however several emerging therapeutics are currently in clinical trial testing utilizing novel targets. In the R/R setting, enasidenib now offers a noncytotoxic option for patients with IDH2 mutations via its differentiating effect. Venetoclax targets BCL2 and is in late phase combination trials for patients not eligible for induction. Multi-kinase and specific, potent inhibitors of FLT3, including sorafenib, crenolanib, gilteritinib, and quizartinib, are also in late phase trials. Some may be best suited for adjunct upfront usage with chemotherapy like midostaurin, while others may have single agent activity in the R/R setting. Adoptive cell therapy and antibody-based immunotherapy are novel approaches earlier in development that aim to improve anti-leukemia T-cell function. Certainly, the AML landscape is now already dramatically changed, and much promise awaits in the years to come.

Acknowledgements

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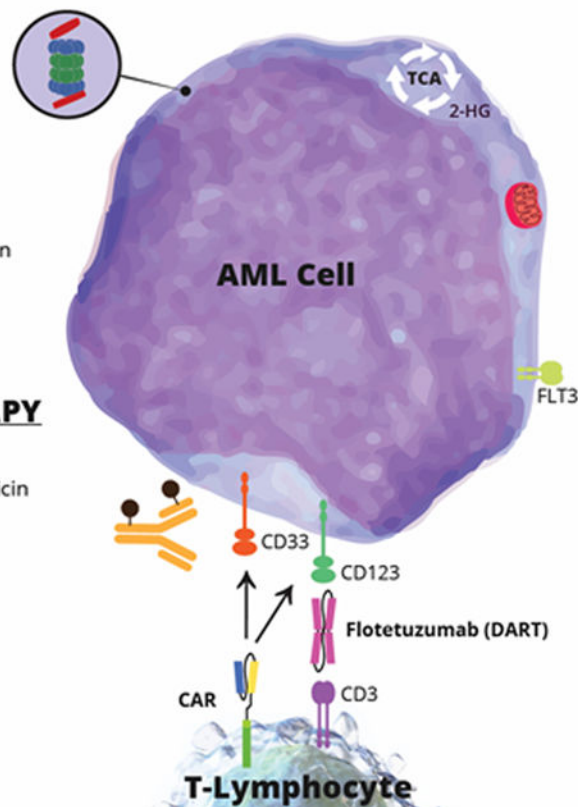
Figure 1.

Novel AML Targets and Therapies

Abbreviations: NEDD-8, neural precursor cell expressed, developmentally down-regulated 8-activating enzyme; IDH, isocitrate dehydrogenase; BCL2, B-cell Lymphoma 2; FLT3, fms like tyrosine kinase 3; CAR, chimeric antigen receptor; DART, dual-affinity re-targeting antibody.

Table 1:

New Targets for Novel AML Therapies

Target	Frequency in AML	Prognostic Impact	Role in Leukemogenesis
FLT3 (FLT3-ITD/ FLT3-TKD)[12]	Mutated in 20-37% (30% ITD and 7% TKD)	Associated with unfavorable outcome in some patients	Leads to production of proteins that circumvent ligandmediated activation, and cause factor-independent growth
CD33[13]	Expressed in approximately 85-90%	Outcomes are dependent on coexisting mutations	Not applicable; however, of note, CD33 is highly expressed on most AML blast cells and less on normal hematopoietic cells
IDH1, IDH2[12, 14]	IDH1 mutated in 6-16%; IDH2 mutated in 8-19%	Conflicting evidence on prognostic significance	Leads to synthesis of 2-hydroxyglutarate, which results in DNA and histone hypermethylation and ultimately impedes cellular differentiation
BCL2[15, 16]	Wide degree of heterogeneity in expression (mean expression of 23% in one study, but as high as 71% in a different study)	Outcomes are dependent on coexisting mutations	Overexpression of gene can lead to impaired cellular apoptosis
NEDD8 Activating Enzyme (NAE) [17]	Variable expression in all cell lines including AML stem cells	Unknown impact on outcomes	Leads to protein (including proapoptotic protein) degradation and DNA repair to prevent cellular instability
CD123[18, 19]	Expressed in between 44-88% of AML blasts	CD123 expression is associated with high risk disease and disease progression	Overexpression of CD123 may lead to resistance to apoptosis

Abbreviations: AML, acute myeloid leukemia; FLT3, fms like tyrosine kinase 3; FLT3-ITD, fms like tyrosine kinase 3- internal tandem duplication; FLT3-TKD, fms like tyrosine kinase 3-tyrosine kinase domain; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; BCL2, B-cell Lymphoma 2; NEDD8, Neural Precursor Cell Expressed, Developmentally Down-Regulated 8

Table 2:

Newly-Approved AML Therapies

Therapy	Indication	Key Outcomes	Key Adverse Events	Ref#
Midostaurin	Newly diagnosed FLT3+ AML	Per the CALGB 10603/RATIFY trial, median OS of 74.7 months in the midostaurin group versus 25.6 months in placebo group	Grade 3 or greater rash/ desquamation and nausea	[20]
CPX-351	Newly diagnosed therapy-related AML or AML with myelodysplastic-related changes	Phase III trial comparing CPX-351 with 7+3 chemotherapy showed superior OS (9.56 months versus 5.95 months) in the CPX-351 treatment arm, as well as CR and CRi response rates (47.7% versus 33.3%)	Hemorrhage, neutropenia, hypersensitivity reactions	[30]
Gemtuzumab ozogamicin	Newly diagnosed CD33+ AML or R/R CD33+ AML	The 2012 ALFA-0701 study compared low fractionated-dose GO with standard first-line chemotherapy, and found an improvement in median OS in the GO arm (34 months versus 19.2 months, p = 0.046)	Transaminitis, and veno-occlusive disease (rare but severe complication)	[24]
Enasidenib	IDH2-mutant R/R AML	CR or CRi in 26.6% of patients, with an additional 12% of patients with partial response for an overall response rate of 38.5%. Median OS was 9.3 months overall, with a median OS of 19.7 months in patients with CR	Hyperleukocytosis, and IDH-inhibitor-associated differentiation syndrome (IDH-DS)	[31]

Abbreviations: FLT3, fms like tyrosine kinase 3; AML, acute myeloid leukemia; OS, overall survival; CR, complete remission; CRi, complete remission with incomplete hematologic response; R/R, relapsed/refractory; IDH2, isocitrate dehydrogenase 2.

Table 3:

Select Novel AML Therapies in Clinical Trials

Therapy	Type	Target	Development Status	Potential Patient Population
Venetoclax	Small molecule inhibitor	BCL2	Randomized phase III	Newly diagnosed ineligible for standard induction
Sorafenib	Small molecule kinase inhibitor	Multikinase including FLT3	Randomized phase II	FLT3-mutated newly diagnosed, R/R, and possible maintenance
Gilteritinib	Small molecule kinase inhibitor	FLT3-ITD/FLT3-TKD/AXL	Randomized phase III	FLT3-mutated, both newly diagnosed and R/R
Crenolanib	Small molecule kinase inhibitor	FLT3-ITD/FLT3-TKD	Randomized phase III	FLT3-mutated, both newly diagnosed and R/R
Quizartinib	Small molecule kinase inhibitor	FLT3-ITD	Randomized phase III	FLT3-mutated, both newly diagnosed and R/R
Ivosidenib	Small molecule	IDH1	Randomized Phase III	Newly diagnosed IDH1-mutated ineligible for intensive therapy
Pevonedistat	Small molecule inhibitor	NAE	Randomized phase III	Newly diagnosed low blast count(20-30%)
CAR-T cells	Adoptive cell therapy	CD33/CD123/others	Phase I	R/R
Flotetuzumab	DART	CD123	Phase I	R/R

Abbreviations: BCL2, B-cell Lymphoma 2; FLT3-ITD, fms like tyrosine kinase 3- internal tandem duplication; FLT3-TKD, fms like tyrosine kinase 3- tyrosine kinase domain; IDH1, isocitrate dehydrogenase 1; NAE, Nedd8-activating enzyme; CAR-T, chimeric antigen receptor T-cells; DART, dual-affinity re-targeting antibody.