8 Novel and Investigational Therapies in Acute Myeloid Leukemia

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8.1 Introduction

Acute myeloid leukemia encompasses a heterogeneous group of blood and bone marrow neoplasms that arise from the expansion of hematopoietic cell clones carrying recurrent cytogenetic and/or molecular abnormalities [1]. Overall outcomes of AML patients are generally poor with only 28.3% of patients alive at 5 years, though outcomes are very heterogeneous depending on the disease subtype and cytogenetic/molecular risk [2]. Cytogenetic risk stratification remains one of the most important prognostic factors in AML though approximately 40–50% of AML patients have a normal karyotype, but these patients' overall outcomes vary depending on their molecular profile. The 2017 European Leukemia Net (ELN) risk stratification for AML incorporated a few molecular aberrations that may improve risk stratification of AML [3]. Until recently, little has changed in the management and treatment options for patients with AML. The standard intensive chemotherapy for "medically fit" AML patients remained mainly dependent on the backbone of the combination of cytarabine and anthracycline; however, several novel drugs have received regulatory approval in AML in the last couple of years, and many novel therapeutic targets and strategies are currently under development. Thus, the landscape of therapy has evolved to include targeted therapies (midostaurin, enasidenib, ivosidenib, and venetoclax), liposomal encapsulated cytarabine plus daunorubicin (CPX-351), and monoclonal antibodies/antibody–drug conjugates (gemtuzumab ozogamicin and others) [4–9]. This chapter summarizes the data published on these novel approved agents and highlights some of the investigational agents that are currently in development.

8.2 The Molecular Landscape of AML

Genome sequencing efforts of samples from AML patients have highlighted the genomic landscape of AML and recognized its complex structure, and some of these mutations have a significant independent impact on AML survival and response to therapy [10–12]. More importantly, these studies have led the way to develop effective targeted therapies for certain mutations. Obtaining a genomic panel of several genes using next-generation targeted deep sequencing became routine practice for AML at diagnosis and after their relapse. Such a panel carries significant information that can alter patients' prognosis and treatment recommendations.

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The Cancer Genome Atlas Project evaluated the genomic alterations in 200 patients with de novo AML and noted the presence of one or more driver mutations in each AML sample. Genomic abnormalities were classified into various functional groups. Genes affecting signaling pathways were most common constituting 59% (e.g., *FLT3*, *KIT*, *KRAS/NARS*, and *PTPN11*); other common functional groups include DNA-methylation genes (44%) (e.g., *DNMT3A* or *DNMT3B*, *DNMT1*, *TET1*, *IDH1/2*) and chromatin modifying genes (30%) (e.g., *KMT2A* fusions, *ASXL1*, *EZH2*, *KDM6A*). Nucleophosmin gene (*NPM1*) mutations occurred in 27% of patients. Other less common genomic functional groups include transcription-factor gene mutations (22%), tumor-suppressor genes (16%), spliceosome-complex genes (14%), and cohesin-complex gene mutations (13%) [13].

Other studies have focused their efforts on investigating the genomic landscape in therapy-related and secondary AML. The presence of spliceosome gene mutations such as *SRSF2*, *SF3B1*, *U2AF1*, and *ZRSR2* and mutations in *ASXL1*, *EZH2*, *BCOR*, or *STAG2* was >95% specific for secondary AML when compared to de novo disease [14]. Adjusting for clinical variables such as age, karyotype, and white blood cell count was shown to change the specificity of some of these mutations in another study of secondary AML [15].

Importantly, the genomic landscape of AML demonstrates some of the disease heterogeneity and the co-occurrence of some of these mutations could have implications on response to therapy and patient outcomes.

8.3 Novel Therapies Receiving Regulatory Approval

In the last 2 years, a total of eight new drugs have been FDA approved for the treatment of AML patients. In April 2017, the U.S. Food and Drug Administration (FDA) approved midostaurin, a multi-kinase *FLT3* inhibitor, for newly diagnosed patients with *FLT3*-positive AML. This was the first targeted therapy approved in AML demonstrating a clear survival benefit when combined with induction chemotherapy vs. chemotherapy alone [9]. About 4 months later, single-agent enasidenib, a first in class oral inhibitor of *IDH2* was approved for patients with relapsed/refractory AML carrying an *IDH2* mutation [8]. In September 2017, the monoclonal antibody drug conjugate targeting CD33, gemtuzumab ozogamicin was re-approved, after having been taken off the market in 2010, in combination with induction chemotherapy for newly diagnosed patients with AML or as a single agent in the relapsed/refractory setting [6, 16]. The liposomal encapsulated combination of cytarabine plus daunorubicin (CPX-351) was approved for newly diagnosed therapy-related AML or AML with myelodysplasia-related changes (AML-MRC) where it demonstrated a survival advantage over standard 7+3 induction chemotherapy [7]. In 2018, a few additional AML drugs received FDA approval, these include ivosidenib (*IDH1* inhibitor) single-agent oral therapy in relapse/refractory IDH1 mutated AML [4], gilteritinib (*FLT3* inhibitor) as single-agent oral therapy for relapsed/refractory FLT3 mutated AML [17], and Venetoclax, an oral BCL-2 inhibitor, which received accelerated approval for newly diagnosed older adults unfit for standard induction chemotherapy in combination with low-dose cytarabine or hypomethylating agents (azacitidine or decitabine) after showing promising results in early phase clinical trials [5, 18]. Finally, glasdegib, a smoothened hedgehog inhibitor, received approval in combination with low-dose cytarabine (LDAC) after showing a survival advantage when compared to cytarabine alone [17]. In the next few sections of this chapter, the specific outcomes and results of these trials will be summarized and some of the investigational agents being evaluated in clinical trials highlighted (Table 8.1).

Table 8.1 Selected clinical trials using investigational agents in AML

Investigational agents	Upfront vs. R/R	Single agent vs. combination therapy	Trial phase	Clinical trial identifier
Hypomethylating agents or HDAC inhibitors				
Guadecitabine	Upfront	Single agent	III	NCT02348489
Pracinostat	Upfront	Combined with azacitidine	III	NCT03151408
Monoclonal antibodies				
Vadastuximab talirine	Upfront	Combined with azacitidine	III	NCT02785900
Talacotuzumab	Upfront	Combined with decitabine	II/III	NCT02472145
AMG-330	R/R	Single agent	I	NCT02520427
ARGX-110	Upfront	Combined with azacitidine	I/II	NCT03030612
IMGN632	R/R	Single agent	I	NCT03386513
Hu5F9-G4	R/R	Single agent and in combination with azacitidine	I	NCT03248479
FLT3 inhibitors				
Gilteritinib	Upfront	Alone or combined with azacitidine (two arms)	II/III	NCT02752035
Gilteritinib	R/R	Single agent	III	NCT02421939
Crenolanib	Upfront	Combined with chemotherapy	III	NCT03258931
Crenolanib	R/R	Combined with chemotherapy	III	NCT03250338
Quizartinib	R/R	Single agent	III	NCT02039726
IDH1/2 inhibitors				
Ivosidenib	Upfront	Combined with azacitidine	III	NCT03173248
Enasidenib	R/R	Single agent	III	NCT02577406
BCL-2 inhibitor				
Venetoclax	Upfront	Combined with azacitidine	III	NCT02993523
Venetoclax	Upfront	Combined with low dose cytarabine	III	NCT03069352

8.4 Novel Cytotoxic Therapy Formulations

CPX-351 is a novel liposomal encapsulated formulation of cytarabine and daunorubicin (anthracycline) that maintains a fixed synergistic molar ratio of 5:1 between the molecules. Early preclinical development of CPX-351 showed high efficacy of this novel formulation before moving it into the clinical setting [19].

Following the phase I study, CPX-351 was tested in two randomized, multicenter, phase II clinical trials. The first clinical trial compared CPX-351 as a salvage chemotherapy for AML patients age 18–65 years in the first relapse. Response rates were similar, and there was no improvement in overall survival (OS) (hazard ratio (HR) for death, 0.75; $P = 0.19$) or event-free survival (EFS) (HR, 0.66; $P = 0.08$). One year OS was 36% vs. 27% for CPX-351 vs salvage therapy, respectively ($P = 0.33$). Subset analysis of poor risk patients with a high European Prognostic Index (EPI) demonstrated an overall survival advantage for CPX-351 vs salvage chemotherapy ($P = 0.02$, HR = 0.55) [20]. The second randomized phase II trial compared CPX-351 to standard 7+3 induction chemotherapy in newly diagnosed patients with AML age 60–75 years. Results demonstrated an improvement in overall response rate (66.7% vs 51.2%, $P = 0.07$) with no difference in EFS or OS. A planned analysis of the high-risk AML cohort (secondary AML, complex cytogenetics, or age 70–75 years) however, showed a significant improvement in response rates (57.6% vs 31.6%, $P = 0.06$), as well as prolongation of EFS (HR 0.59, $P = 0.08$) and OS (HR = 0.46, $P = 0.01$) [21]. Given the promising outcomes in patients with secondary or therapy-related AML (t-AML), this provided the rationale for the design of the randomized phase III clinical trial that led to its regulatory approval in the frontline setting. In this landmark trial, 309 patients (age 60–75 years) with t-AML or AML-MRC

based on the WHO 2008 definition, were randomized to receive CPX-351 vs 7+3 (cytarabine + daunorubicin) induction chemotherapy. CPX-351 was dosed at 100 U/m^2 (100 mg/m^2 cytarabine and 44 mg/m^2 daunorubicin) on days 1, 3, and 5 of the induction cycle. The trial allowed for another induction cycle for patients with no response to the first induction. Response rates were higher in CPX-351 vs. 7+3 (47.7% complete remission/CR with incomplete count recovery vs. 33.3% respectively, P = 0.016). Importantly, overall survival was improved by about 4 months (9.6 vs. 5.9 months respectively, the hazard ratio (HR) for death 0.69, P = 0.005). Toxicities were similar in both groups, and both 30- and 60-day mortality were lower using CPX-351 (5.9% vs. 10.6% and 13.7% vs. 21.2%, respectively), but not statistically significant between treatment arms [7]. The FDA and the European Medicines Agency (EMA) have approved CPX-351 based on these results for patients with t-AML or AML-MRC. There are, however, some limitations for the widespread use of CPX-351. These include its higher cost compared to 7+3 and the delay in obtaining cytogenetic results (therefore missing a portion of patients with AML-MRC), a group which constituted 26.9% in this trial. It is worth noting that in a post hoc exploratory analysis landmarked at the time of transplant, patients receiving induction with CPX-351 had better overall survival than was observed in the control arm (not reached vs. 10.8 months for 7+3, HR 0.46, P = 0.009).

8.5 Novel Hypomethylating Agents and HDAC Inhibitors

Treatment for older adults with AML unfit to receive intensive chemotherapy remains a challenge; historically, options for those patients have included hypomethylating agents (azacitidine and decitabine), low-dose cytarabine (LDAC), or best supportive care (BSC). The median survival for patients treated with azacitidine was 10.4 months compared to 6.5 months for 7+3/LDAC/BSC arm, P = 0.1 and median OS for decitabine (in patients with poor/intermediate risk cytogenetics) was 7.7 months compared to 5.0 months for 7+3/LDAC/BSC arm, HR 0.85, P = 0.11 [22, 23]. Based on these data, treatment with hypomethylating agents has been widely adopted as a standard of care for newly diagnosed patients unfit to receive standard induction chemotherapy given the safety and tolerability profile. Guadecitabine (SGI-110), a second-generation hypomethylating agent, is currently under development. Guadecitabine is a dinucleotide of decitabine and deoxyguanosine and has a longer half-life than azacitidine or decitabine. Guadicitabine has been studied in early phase clinical trials in both newly diagnosed and relapsed/refractory AML [24, 25]. Patients were treated using three different dosing schedules. The first group received guadecitabine 60 mg/m^2 for 5 days, the second group received 90 mg/m^2 for 5 days, and the third group received 60 mg/m^2 for 10 days. Cycles were repeated every 28 days. Response rates and tolerability were compared in each treatment arm. There were no significant differences in the composite complete remission (CRc) rates between the arms for newly diagnosed, treatment naïve patients (CRc 50–59%). In the relapsed/refractory setting, CRc was higher using a 10- vs. 5-day schedule. A phase III randomized controlled trial (ASTRAL-1) of guadecitabine vs. physician's choice of standard therapy (azacitidine, decitabine, or LDAC) in treatment naïve adult patients with AML did not meet the co-primary endpoints based on failure to improve complete response rate (P > 0.04) and overall survival (P > 0.01). Currently, ASTRAL-2 is an ongoing phase III trial examining guadecitabine in relapsed/refractory AML (NCT02920008).

Histone deacetylase (HDAC) inhibitors have been investigated in myeloid malignancies and were shown to exert their effects by the regulation of histone and non-histone protein acetylation [26, 27]. While most HDAC inhibitors have modest activity as single agents, pracinostat, an oral HDAC inhibitor, has shown promising results when used in combination with HMA therapy [28, 29]. Pracinostat plus azacitidine was used upfront in a cohort of 50 patients and showed a complete remission rate of 42%. The primary composite endpoint included CR, CR

with incomplete count recovery (CRi), and morphologic leukemia-free state was 54% [30]. The 1 year overall survival rate was 62% [31]. The combination is currently being evaluated compared to azacitidine plus placebo in a randomized double-blinded phase III trial for newly diagnosed older adults with AML unfit for induction chemotherapy (NCT03151408) (Table 8.1).

8.6 Monoclonal Antibodies in AML

Monoclonal antibody target cell surface antigens that are preferentially expressed on myeloid cells or blast populations. Multiple targets are currently being investigated such as antibodies targeting CD33, CD123, and CD47 among others [32]. The mechanism of actions of monoclonal antibodies may vary to include cell-mediated cytotoxicity or in an antibody–drug conjugate (ADC) mechanism, where cytotoxic compounds are introduced to cells via target antigen. Gemtuzumab ozogamicin (GO) is an ADC that targets CD33-positive cells. The anti-CD33 antibody is linked to *N*-acetyl gamma calicheamicin. Once bound to CD33, the antigen/ADC is internalized and calicheamicin released intracellularly leading to direct DNA damage and cell death (Fig. 8.1). GO was initially approved by the FDA in 2000 and was then taken off the market in 2010 when the confirmatory phase III clinical trial (SWOG S0106) failed to show clinical benefit. GO has

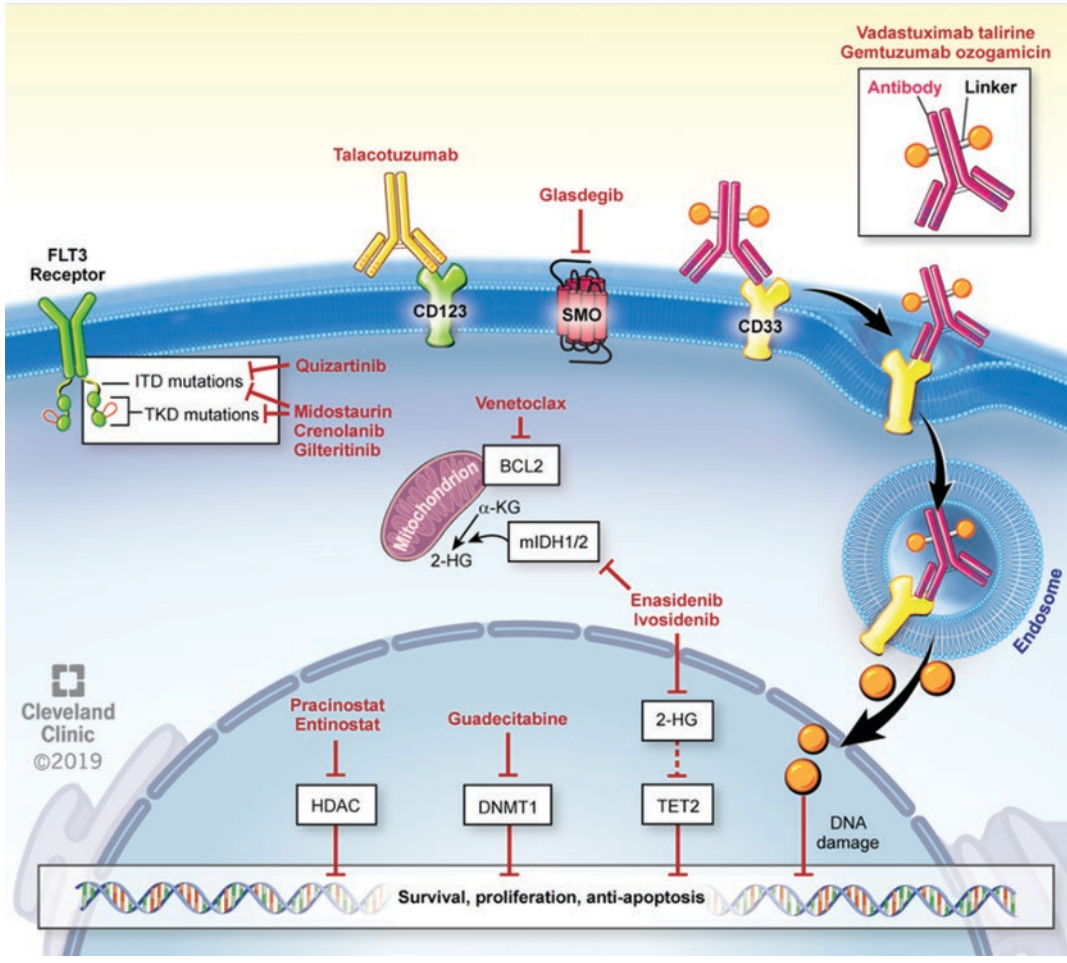

Fig. 8.1 Novel and investigational therapies in AML

been re-approved by the FDA for use in newly diagnosed CD33-positive AML in combination with chemotherapy (7+3) or as a single agent in the relapsed/refractory setting. The approval was based on a meta-analysis of 3325 patients treated with GO [6]. The pivotal trial, ALFA 0701, was a phase III randomized clinical trial of 271 patients with newly diagnosed AML (aged 50–70 years), patients received standard induction therapy (cytarabine + daunorubicin) alone or in combination with gemtuzumab. GO was given in fractionated dosing 3 mg/m^2 on days 1, 4 and 7 of the induction chemotherapy cycle. Patients achieving a CR/CRp went on to receive 5+2 consolidation plus GO at 3 mg/m^2 on day 1 of each of the two consolidation cycles.

The event-free survival (EFS) was 17.1% in the control group vs. 40.8% for GO at 2 years, HR 0.58, 0.43–0.78; $P = 0.0003$), overall survival was 41.9% vs. 53.2%, respectively (0.69, 0.49–0.98; $P = 0.0368$); however, the survival advantage was no longer significant in the long-term follow-up [33, 34]. In the large meta-analysis using data from five randomized trials (3325 patients), the addition of GO did not affect CR/CRi rate; however, reduced risk of relapse (OR 0.81, 0.73–0.90; $P = 0.0001$) and showed a 5-year OS advantage (OR 0.90, 0.82–0.98; $P = 0.01$). However, the survival advantage was largely driven by patients with good risk cytogenetics where the OS at 6 years was improved by 20·7%; OR for survival = 0·47, $P = 0.0006$. Given those results, the addition of GO has been largely adopted in favorable risk AML (i.e., core binding factor leukemia or AML with t(8;21) and inv16/t(16;16) in the upfront setting [6].

Another antibody–drug conjugate that targets CD33 is vadastuximab talirine (SGN-CD33A). The antibody is attached to a DNA binding agent, a pyrrolobenzodiazepine (PBD) dimer via a cleavable linker. The ADC showed promising activity in early phase clinical trials; however, the phase III CASCADE trial randomizing patients to hypomethylating therapy with or without SGN-CD33A was terminated early due to an increased number of deaths using the combination arm in newly diagnosed patients with AML. The pharmaceutical company has suspended patient enrollment and treatment in all of its vadastuximab talirine clinical trials including the ongoing phase I/II clinical trial in frontline high-risk myelodysplastic syndromes [35–38].

CD123 is a cell surface marker that is highly and preferentially expressed on leukemic blast cells and leukemic stem cells. Talacotuzumab is an Fc engineered anti-CD123 monoclonal antibody that activates antibody-dependent cellular cytotoxicity (ADCC) mediated by natural killer cells (NKs). It was used as a single agent after hypomethylating therapy failure with limited efficacy as a single agent. A phase II/III study of talacotuzumab in combination with decitabine vs. decitabine alone in older patients with AML ineligible for intensive chemotherapy has completed accrual, and the results of the trial are still pending. Talacotuzumab is administered by intravenous infusion at 9 mg/kg on days 8 and 22 of a 28-day cycle in combination with decitabine at the standard approved dose of 20 mg/m^2 on days 1–5 each cycle (NCT02472145).

IMGN632 is another CD123-targeting antibody–drug conjugate with a novel humanized anti-CD123 antibody joined, via a peptide linker, to a unique DNA-alkylating payload of IGN (indolinobenzodiazepine pseudodimer). In a phase I trial (NCT03386513) in patients with R/R AML, 12 patients received dose escalation of the drug. No DLTs have been observed at doses up to 0.18 mg/kg (cohort 4), and no discontinuations due to an AE have occurred. The most commonly observed treatment-emergent AEs of any grade were primarily gastrointestinal (decreased appetite, diarrhea, nausea; 25–42%), hematologic (febrile neutropenia; 42%), or vascular (peripheral edema, hypotension, sinus tachycardia; 25–33%). The most frequent grade 3+ AEs were febrile neutropenia (five patients; 42%) and lung infection (three patients; 25%); none of these events were considered related to IMGN632. In 12 evaluable patients, four (33%) achieved an objective response, including one complete remission (CR) and three complete remissions with incomplete recovery (CRi). The trial is still ongoing and further analyses will be presented in the future.

Other antibodies include AMG 330, an anti-CD33/CD3 bispecific T-cell engaging (BiTE) antibody composed of two single-chain variable fragments, where one is directed against CD33-positive leukemia cells and the other directed against CD3 found on cytotoxic T-lymphocytes (CTL) leading to CTL-mediated cell death of CD33-positive cells. A Phase I dose escalation study of AMG 330 in patients with relapsed/refractory AML enrolled 35 patients in 12 dose cohorts. The median number of cycles of AMG 330 was 1 (range, 1–6), and 89% of patients discontinued treatment. The most common reason for treatment discontinuation was disease progression (n = 24). The most common serious adverse event was cytokine release syndrome (CRS) occurring in 11 patients. Dose-limiting toxicities with the initial target dose of 480 μg/day were grade 2 CRS and grade 4 ventricular fibrillation, leading to a decrease in target dose to 240 μg/day. A total of four patients achieved CR/CRi at target doses of 120–240 μg/day [39].

CD70 is a cell surface marker that was noted to be upregulated with HMA therapy which could potentially contribute to HMA resistance. Based on preclinical work, a phase I/II trial combining azacitidine with ARGX-110, an anti-CD70 monoclonal antibody, in newly diagnosed AML patients unfit for intensive chemotherapy was designed (NCT03030612). The preliminary data of the first 12 patients treated showed no dose-limiting toxicity and high overall response rates (combining CR, CRi, PR, and MLFS) of 92% with 9/11 patients (82%) achieving CR/CRi [40]. Thus, monoclonal antibodies this far are showing clinical efficacy in combination therapy and not as single agents.

Another important new target in AML is CD47. CD47, also known as integrin-associated protein, is a ubiquitously expressed 50 kDa cell surface transmembrane Ig superfamily member. CD47 interacts with integrins (e.g., αvβ3, αIIbβ3, and α2β1) and thrombospondin-1 and serves as a ligand for signal regulatory protein alpha (SIRPα). CD47 is overexpressed in several solid tumors as well as hematologic malignancies such as AML. Several agents such as Hu5F9-G4 (Magrolimab), CC-90002, and others are currently in the development of AML as single agents or in combination with azacyitidine, but preliminary results are promising.

8.7 Targeted Therapies

8.7.1 Fms-Like Tyrosine Kinase 3 (*FLT3*) Inhibitors

FLT3 mutations are among the most common mutations occurring in about one-third of patients with AML. There are two well-characterized *FLT3* mutations, the first is *FLT3*-internal tandem duplications (*FLT3-ITD*) occurring in the juxtamembrane domain which are more prevalent (~25%) and point mutations in the tyrosine kinase domain (*FLT3-TKD*) which occur in 5–7% (Fig. 8.1). Multiple *FLT3* inhibitors have been used in clinical trials, some of which are now FDA approved. *FLT3-ITD* allelic ratio plays a role in prognostication, where the allelic ratio of >0.5 in the absence of *NPM1* mutations, stratifies patients in "adverse-risk" AML per ELN classification. On the contrary, the prognostic relevance of *FLT-TKD* mutations is somewhat controversial [3].

Multi-targeted kinase inhibitors such as sorafenib and midostaurin (first-generation FLT3 inhibitors) have shown in vitro inhibition of FLT3; however, single-agent activity was limited. A randomized phase II placebo-controlled clinical trial in younger adults (age < 60 yeas) with AML which assigned patients to receive sorafenib 400 mg BID in combination with induction chemotherapy showed improvement in 3-year event-free survival (EFS) (22%, 95% CI 13–32) in the placebo group vs. 40% (29–51) in the sorafenib arm (hazard ratio 0.64, 95% CI 0.45–0.91; P = 0.013) without an overall survival benefit. The combination with sorafenib was associated with increased toxicity (grade ≥ 3 adverse events such as fever, diarrhea, bleeding, cardiac events, hand–foot–skin reaction, and rash) [41]. Improvement in OS or EFS was not seen in older adults (age > 60 years) with FLT3-positive AML [42].

Midostaurin is now approved for the treatment of newly diagnosed AML patients in combination with induction and consolidation chemotherapy for all age groups. In early phase trials, midostaurin was used at 50 mg BID vs. 100 mg BID. The higher dose did not move forward largely due to gastrointestinal side effects [43], whereas the 50 mg dosing was well tolerated and showed high efficacy, which led to the design of the landmark trial that led to its approval; the RATIFY trial is a phase III randomized, double-blind, placebo-controlled trial of 717 patients age 18–59 years with newly diagnosed *FLT3*-positive AML which assigned patients to receive induction chemotherapy (daunorubicin plus cytarabine) followed by consolidation chemotherapy with high-dose cytarabine plus midostaurin at 50 mg twice/day or placebo added for 14 days (days 8–21) to induction and each of the consolidation cycles. Patients in remission received midostaurin/placebo maintenance for up to 12 months. Overall survival was significantly longer with midostaurin vs. placebo with a 22% reduction in risk of death (HR = 0.78; one-sided $P = 0.009$). Grade ≥ 3 adverse events were similar between treatment arms; however, nausea ($P = 0.05$), anemia ($P = 0.03$) and rash or desquamation ($P = 0.008$) were more common with midostaurin [9].

More selective second-generation *FLT3* inhibitors have reached later stages (phase III trials) in drug development and include gilteritinib, quizartinib, and crenolanib.

Quizartinib is a very selective FLT3-ITD inhibitor that was tested in a randomized controlled trial vs. salvage chemotherapy for patients with relapsed/refractory *FLT3-ITD*-positive AML. Quizartinib was dosed at 60 mg daily. Prior therapy with midostaurin was allowed. Of 367 patients ≥18 years of age randomized in 2:1 fashion, 245 received quizartinib and 122 patients received salvage chemotherapy. The overall survival was improved by 24% (HR for death = 0.76; 95% CI 0.58–0.98; stratified log-rank test, one-sided $P = 0.018$). Median overall survival was increased by about 7 weeks (OS 27 weeks vs. 20.4 weeks for quizartinib vs. chemotherapy) [44]. Despite this result, quizartinib did not receive FDA approval in the United States and currently is only approved for AML treatment in Japan. Gilteritinib is a selective FLT3 inhibitor that received FDA approval for the treatment of adults with relapsed/refractory AML with *FLT3* mutations. The phase I/II dose-escalation/expansion study demonstrated a maximum tolerated a dose of 300 mg daily due to the development of grade 3 diarrhea and elevated AST with higher doses. Grade 3 or 4 adverse events in that trial included febrile neutropenia (39%), anemia (24%), thrombocytopenia (13%), sepsis (11%), and pneumonia (11%) [17, 45]. In a phase III randomized controlled trial, 138 patients with R/R FLT3-positive AML were enrolled. Patients were treated with gilteritinib 120 mg/day oral continuous dosing. The complete remission (CR) or CR with partial hematologic recovery (CRh) rate was 21% after a median follow-up of 4.6 months. The median overall survival for patients who received gilteritinib was 9.3 months vs. 5.6 months for salvage chemotherapy (HR 0.637 (95% CI 0.490, 0.830), $P = 0.0007$) [46].

Patients treated with *FLT3* inhibitors may develop secondary mutations in D835 or F691 residues which are some of the described mechanisms of resistance [47]. Crenolanib is a potent and selective inhibitor of wild-type and mutant class III receptor tyrosine kinases *FLT3* and *PDGFRα/β*, particularly of D835 mutations [48]. Crenolanib was studied in the upfront setting in combination with chemotherapy with promising results. The preliminary analysis of 26 patients ≥18 years old enrolled in a phase II trial, crenolanib 100 mg TID was administered continuously starting on day 8 until 72 h prior to the next chemotherapy cycle. Consolidation consisted of up to four cycles of high-dose cytarabine with crenolanib starting on day 7 in each cycle. Maintenance crenolanib after consolidation or transplant was given for up to 12 cycles. Out of 25 patients evaluable for response, CR/CRi rate was 96% [49]. Thus, a phase III, randomized, multicenter trial is designed to compare the efficacy of crenolanib vs. midostaurin combined with standard chemotherapy for patients with FLT3-positive newly diagnosed AML (NCT03258931).

8.7.2 Isocitrate Dehydrogenase (*IDH*) 1/2 Inhibitors

Isocitrate dehydrogenases are enzymes that catalyze the conversion of isocitrate to alpha-ketoglutarate (αKG) in the cytoplasm (*IDH1*) or mitochondria (*IDH2*). Mutations in those enzymes are estimated to occur in up to 20% of patients with AML, in which case citrate is catalyzed into an oncometabolite (2-hydroxyglutarate, 2-HG), which leads to a hypermethylated state and a block in cellular differentiation [50–52]. *IDH1* and *IDH2* mutations are not considered prognostic at the time of AML diagnosis and current drug approvals for *IDH1/2* inhibitors (ivosidenib/enasidenib) are for use in the relapsed/refractory setting. However, it is worth noting that in a large study of >1500 patients with AML, $IDH2^{R172}$ mutations were found in 1% of the cohort, patient outcomes with this gene abnormality were more favorable and similar to NPM1-mutated AML [53].

Enasidenib is an oral, first in class, FDA-approved *IDH2* inhibitor. In a phase I/II clinical trial of 239 patients with IDH2-mutated AML, a dose of 100 mg PO daily was given in the expansion phase to 176 patients with relapsed/refractory AML with an overall response rate of 40.3% (19.3% complete remission rate). The median overall survival was 9.3 months in all patients; however, that increased to 19.7 months in 19.3% of patients achieving a CR, which led to regulatory approval [8]. The IDENTIFY trial is a randomized phase III clinical trial investigating its use vs. conventional chemotherapy in older patients with *IDH2*-positive AML (NCT02577406).

Ivosidenib is an oral inhibitor of *IDH1* and was also evaluated in patients with relapsed/refractory AML. In early studies which enrolled 78 patients, the overall response rates were 38.5% with 17.9% of patients achieving a CR. Mutation clearance was observed in 27% of patients in CR [54]. In a larger phase Ib dose escalation/dose expansion trial, 258 patients were enrolled (safety cohort) and 179 of those had relapsed/refractory AML. Grade ≥ 3 adverse events included QT prolongation, *IDH* differentiation syndrome and cytopenia (anemia/thrombocytopenia). A dose of 500 mg daily dosing was chosen for the expansion cohort. Complete remission rate was 21.6% (95% CI 14.7–29.8), ORR 41.6% (95% CI 32.9–50.8), and the MRD negativity in those achieving complete remission or CR with partial hematologic recovery was 21% [4]. *IDH* inhibitors are now being evaluated in combination with induction chemotherapy for newly diagnosed patients with AML.

8.7.3 B-Cell Lymphoma 2 (BCL-2) Antagonists

Cellular death or apoptosis can be induced intrinsically or extrinsically. Intrinsic apoptosis is primarily regulated by BCL2 proteins. BCL-2 is an anti-apoptotic protein that prevents the expression of pro-apoptotic factors such as BCL-2 homology 3 (BH3) domain proteins and is overexpressed in AML. BH3 mimetics, such as venetoclax, inhibit BCL-2 and lead to apoptosis [55, 56].

Venetoclax was used as monotherapy in a phase I trial in patients with relapsed/refractory AML with an overall response rate of 19% [57]. More recently, FDA granted accelerated approval for venetoclax in combination with hypomethylating agents (HMA; azacitidine or decitabine) or low-dose cytarabine (LDAC) for newly diagnosed older adults with AML who are unfit to receive induction chemotherapy. Venetoclax was used at a dose of 600 mg PO in combination with LDAC and led to a CR/CRi rate of 62% with a median OS of 10.1 months [58]. Similarly, in a phase Ib dose-escalation and expansion study, 145 patients were assigned to receive oral venetoclax at 400, 800, or 1200 mg daily in combination with either HMA. In the expansion, 400 mg vs. 800 mg venetoclax was given. The CR/CRi was 73% in the venetoclax 400 mg—cohort with a median OS of 17.5 months (not reached for the azacitidine arm). Adverse events included nausea, diarrhea/constipation, leukopenia, febrile neutropenia, hypokalemia, fatigue, and decreased appetite [59]. Based on the results of this trial, a randomized, placebo-controlled phase III clinical trial of venetoclax

400 mg vs. placebo in combination with azacitidine (NCT02993523 was recently completed confirming the phase II results).

8.8 Summary

The treatment paradigm for acute myeloid leukemia has changed with eight new drug approvals since 2017 and will continue to evolve as many novel agents are in development. Currently, molecularly targeted therapies are limited to inhibitors of FLT3, IDH1, and two mutations. It is important to test for these mutations in the upfront setting, but to also repeat testing for these mutations as they may be acquired at relapse. Monoclonal antibodies targeting cell surface markers include anti-CD33, anti-CD123, and anti-CD70 antibodies among others. Currently, bi-specific T-cell engaging antibodies are being tested in phase I clinical trials. Lastly, BCL-2 inhibition with venetoclax has an important role in the upfront treatment setting of older patients unfit for intensive chemotherapy, in combination with low-dose cytarabine or hypomethylating agents.

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