New agents in acute myeloid leukemia (AML)

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Abstract

Despite expanding knowledge in the molecular landscape of acute myeloid leukemia (AML) and an increasing understanding of leukemogenic pathways, little has changed in the treatment of AML in the last 40 years. Since introduction in the 1970s, combination chemotherapy consisting of anthracycline and cytarabine has been the mainstay of treatment, with major therapeutic advances based on improving supportive care rather than the introduction of novel therapeutics. Over the last decades, there have been extensive efforts to identify specific target mutations or pathways with the aim of improving clinical outcomes. Finally, after a prolonged wait, we are witnessing the next wave of AML treatment, characterized by a more "precise" and "personalized" understanding of the unique molecular or genetic mapping of individual patients. This new trend has since been further facilitated, with four new FDA approvals granted in 2017 in AML therapeutics. Currently, a total of eight targeted agents have been approved since 2017 (as of Jan. 2020). In this review, we will briefly discuss these newer agents in the context of their indication and the basis of their approval.

Key Words Acute myeloid leukemia, New FDA approvals

INTRODUCTION

Acute myeloid leukemia (AML) is a devastating disease, which rapidly becomes fatal if left untreated. Anthracycline and cytarabine-based combination chemotherapy has been the mainstay of treatment since its introduction in the 1970s [1, 2].

Recent advances in genomic technologies have identified that AML is a heterogeneous group of diseases, and the long-term prognosis of AML is significantly different and largely dependent on its own cytogenetics and molecular aberrations [3, 4]. Consequently, there have been substantial changes in the classification and prognostication of AML over the last few decades [5, 6], which are now predicated on identifying genetic features of the individual disease. Concurrently, efforts to discover potential molecular targets have been ongoing.

At the 2017 American Society of Hematology meeting, it was announced that 2017 was a landmark year for the Food and Drug Administration (FDA)-approved therapies for AML, as the U.S. FDA had approved four new therapeutic options for the disease (midostaurin, enasidenib, CPX-351, and gemtuzumab ozogamicin). Subsequently, four additional

drugs (gilteritinib, ivosidenib, venetoclax, and glasdegib) have received U.S. FDA approval for AML [7]. Surprisingly, these advances have occurred only during the recent few years, and we are undoubtedly facing an "innovative era" in the treatment of AML.

In this review, we will focus on the recently approved new targeted agents for the treatment of AML.

NEW AGENTS FOR AML WITH RECENT U.S. FDA APPROVAL

Recently approved drugs for AML and their indication by disease status are listed in Table 1.

MIDOSTAURIN

In April 2017, midostaurin was approved for treatment of naïve *FLT3*-mutant AML, in combination with daunorubicin and cytarabine induction and cytarabine consolidation. Nearly 25–30% and 5–10% of patients with AML harbor an *FLT3*-internal tandem duplication (ITD) and -tyrosine kinase domain (TKD) mutation, respectively [8]. Among the

Table 1. New agents for AML with recent U.S. FDA approval.

	Molecular target	Indication (setting) New	Indication (setting) Rel/ref	Representative trials	OS benefit	FDA approval	In Korea (Jan. 2020)
Midostaurin	FLT3 ITD/TKD	O (combi[a)])		Phase 3 RATIFY	Yes	Apr. 2017	Available
Gilteritinib	FLT3 ITD/TKD		O (single)	Phase 3 ADMIRAL	Yes	Nov. 2018	Not available
Gemtuzumab ozogamicin (GO)	CD33+	O (combi or single)	O (combi or single)	Phase 3 ALFA-0701	No (but benefit in EFS)	Jul. 2017	Available (via KOEDC)
				Phase 3 AML-19	Yes		
				Phase 2 MyloFrance-1	NA		
CPX-351	t-AML AML-MRC	O		Phase 3 (NCT01696084)	Yes	Aug. 2017	Not available
Enasidenib	IDH2		O (single)	Phase 1/2 study (NCT01915498)	NA	Aug. 2017	Not available
Ivosidenib	IDH1		O (single)	Phase 1 dose-escalation/ dose-expansion study (NCT02074839)	NA	Jul. 2018	Not available
Venetoclax	BCL2	O (combi[b)])		Phase 1 dose-escalation study (NCT02203773)	NA	Nov. 2018	Available
				Phase 1/2 study (NCT02287233)	NA		
Glasdegib	Hedgehog signaling pathway	O (combi[c)])		Phase 2 (NCT01546038)	Yes	Nov. 2018	Not available

[a)]Midostaurin in combination with daunorubicin and cytarabine induction and cytarabine consolidation.
[b)]Hypomethylating agents (HMA) such as decitabine or azacitidine with venetoclax (400 mg); low dose Ara-C (LDAC) with venetoclax (600 mg).
[c)]Glasdegib and LDAC.
Abbreviations: BCL2, B-cell lymphoma 2; EFS, event-free survival; FLT3, FMS-like tyrosine kinase 3; IDH, isocitrate dehydrogenase; ITD, internal tandem duplication; KOEDC, Korea Orphan & Essential Drug Center; NA, not assessable; OS, overall survival; rel/Ref, relapsed or refractory; t-AML, therapy-related AML; AML-MRC, AML with myelodysplasia related changes; TKD, tyrosine kinase domain.

mutation locations, *FLT3-ITD* AML often presents hyper-leukocytosis [9, 10] and is a known marker of adverse prognosis. However, the prognostic implication of *FLT3-TKD* mutation remains unclear [11]. Based on the RATIFY trial (randomized AML trial in FLT3-mutated adults younger than 60 years old) [12, 13], in which 717 patients were randomly assigned to chemo +/- midostaurin after screening approximately 3,300 patients, midostaurin was approved by the U.S. FDA after demonstrating a survival benefit in AML patients with mutated *FLT3-ITD* or *TKD*. This was the first FLT3 inhibitor approved in AML, breaking new ground for the trend of precision medicine in AML treatment.

GILTERITINIB

Gilteritinib, for use as a single agent, was approved for relapsed or refractory (R/R) *FLT3-ITD* and/or *FLT3-TKD* mutant AML in November 2018. As mentioned earlier, nearly one-third of AML patients have an activating mutation in *FLT3*. Given that the *FLT3* mutation is frequently observed and strongly associated with relapse and survival in AML, many novel agents have attempted to treat AML harboring the *FLT3* mutation [8, 11, 12]. Gilteritinib, a second-generation *FLT3* inhibitor, is characterized by highly specific and potent inhibition of *FLT3*, with narrower kinome profiles than first-generation *FLT3* inhibitors such as midostaurin [14, 15]. The approval of this drug in AML was based on

the phase 3 ADMIRAL trial [16], which demonstrated that gilteritinib significantly prolongs overall survival in *FLT3* mutated relapsed/refractory AML when compared to comparative salvage chemotherapy arms.

GEMTUZUMAB OZOGAMICIN

In July 2017, gemtuzumab ozogamicin (GO), in combination with daunorubicin and cytarabine or as a single agent, was approved in adults for the treatment of newly diagnosed *CD33*-positive AML. Additionally, the FDA approved GO in R/R *CD33*-positive AML in adults and pediatric patients at least two years of age. GO is a recombinant, humanized anti-CD-33 antibody conjugated to the intracellular toxin, calicheamicin [17]. In May 2000, this drug originally received accelerated approval for *CD33*-positive AML patients (60 yr or older) experiencing their first relapse, and in those not considered candidates for other cytotoxic chemotherapy [18]. Of note, Go combined with attenuated conventional chemotherapy was feasible in elderly patients with AML in Korea [19, 20]. Subsequently, in 2010, it was voluntarily withdrawn from the market due to failure to verify prior efficacy data, as well safety concerns, including a high number of early deaths and hepatic veno-occlusive disease (VOD). Interestingly, however, this drug has remained in the Japanese market based on an individual approach with Pfizer's compassionate use program, which reflects the critical unmet

need for novel agents in AML treatment. Indeed, GO with different dosing and different schedules remained of great interest among AML clinicians, resulting in independent investigators conducting investigator-initiated clinical trials, including ALFA- 0701 (phase 3 study of GO with daunorubicin and cytarabine in 50–70 aged untreated AML) [21], AML-19 (phase 3 study of single-agent GO in newly diagnosed elderly AML) [22], and MyloFrance-1 (phase 2 open-label study of single-agent GO as induction therapy in relapsed AML) [23]. These studies formed the basis for the reapproval of GO, demonstrating an improved event-free survival (EFS), overall survival (OS), or relapse-free survival (RFS). The current approval has been granted for a lower dose "fractionated" schedule rather than the dose originally approved by the FDA (2 doses of 9 mg/m^2 each on days 1 and 8), aimed at a different target population. Currently, the widely accepted protocol of GO is 3 mg/m^2 on days 1, 3, and 5; this reduced and fractionated dose schedule seems to increase tolerance and decrease drug-related toxicity such as VOD [24, 25].

CPX-351

In August 2017, CPX-351 was approved for newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). CPX-351 is a liposomal formulation that delivers a 5:1 fixed-molar ratio of daunorubicin and cytarabine [26, 27]. The approval was based on results of a phase 3 clinical trial in 309 patients with either t-AML or AML-MRC, which evaluated the efficacy and safety of CPX-351 compared to conventional cytarabine and daunorubicin induction [28]. In this study, CPX-351 demonstrated an improvement in OS, with a median OS of 9.56 months for the CPX-351 arm versus 5.95 months for the conventional chemotherapy arm. Although the trial was conducted only in patients aged 60 to 75 years, the FDA approved CPX-351 for use in all adults with no age restrictions.

ENASIDENIB AND IVOSIDENIB

Enasidenib, for use as a single agent, was approved by the FDA in August 2017 for R/R AML with the isocitrate dehydrogenase-2 (IDH2) mutation. In July 2018, ivosidenib was also approved as a single agent in IDH1-mutated R/R AML. Enasidenib [29-31] and ivosidenib [32-34] are small molecule inhibitors targeting IDH2 and IDH1, respectively. Isocitrate dehydrogenase (IDH) plays a key role in converting isocitrate to α-ketoglutarate (α-KG), demonstrating the three different isoforms of IDH1, 2 and 3. The IDH mutation results in a neomorphic enzyme, which can result in the abnormal accumulation of the oncometabolite R-2-hydroxyglutarate (R-2-HG) and promote leukemogenesis [35]. Notably, nearly 6–10% of AML patients bear a mutation in IDH1, and mutations in IDH2 are observed in 9–13% of AML patients [36-38]. However, reports on the prognostic potential of IDH1 and IDH2 mutations have been inconsistent. The approval of enasidenib in AML was based on a phase 1/2 study [31]. In this study, patients with IDH2 mutated R/R AML, treated with single-agent enasidenib, demonstrated a response rate of 40.3% [complete remission (CR) rate of 19.3%], and median OS of 9.3 months. Similarly, ivosidenib was approved based on a large phase 1 dose-escalation/dose-expansion trial [32]. In this study, IDH1 mutated R/R AML patients treated with single-agent ivosidenib demonstrated a response rate of 41.6% [composite CR (cCR) rate of 30.4%] and median OS of 8.8 months. As an adverse event of special interest, differentiation syndrome was observed in patients treated with enasidenib (7%) and ivosidenib (3.9%). Reportedly, the IDH-differentiation syndrome is manageable by interrupting medication and treatment with glucocorticoids, with or without hydroxyurea [39, 40].

VENETOCLAX

Venetoclax, in combination with azacitidine or decitabine or low dose cytarabine, received accelerated FDA approval in Nov 2018 for newly diagnosed AML (age 75≥yr or "unfit" patients). Venetoclax is an orally active, and potent small molecule inhibitor targeting B-cell lymphoma 2 (BCL2) [41]. The approval of this new agent was based on two open-label non-randomized trials of Study M14-358 (NCT02203773) [42] and Study M14-387 (NCT02287233) [43]. In M14-358 (Phase 1 dose-escalation study), venetoclax in combination with azacitidine or decitabine was evaluated in newly diagnosed elderly (≥65 yr), unfit AML patients, with venetoclax doses of 400, 800, or 1,200 mg daily. The median age of enrolled patients was 74 years, and the poor-risk cytogenetics comprised 49%. Promising results were observed with cCRs of 67% (all doses) and 73% (venetoclax 400 mg), the median duration of cCR was 11.3 months and the median OS was 17.5 months. Unexpectedly, the results demonstrated that patients with poor-risk cytogenetics and those at least 75 years of age reported cCR rates of 60% and 65%, respectively. Additionally, M14-387 (NCT02287233) was another notable study that contributed to the accelerated approval of venetoclax. This phase I/II study evaluated the safety and preliminary efficacy of venetoclax (600 mg) with low dose cytarabine (LDAC) in untreated elderly (≥60 yr) or unfit AML patients. The median age of enrolled patients was 74 years and the poor-risk cytogenetics comprised 32%. Nearly one-third of patients (29%) had received prior hypomethylating agents (HMA) treatment. In this difficult-to-treat population, 54% achieved cCR, median OS was 10.1 months, and the median response duration was 8.1 months. Based on the aforementioned trials [42, 43], the recommended venetoclax dose depends on the combination regimen: 400 mg daily in combination with HMA and 600 mg daily in combination with LDAC [7].

GLASDEGIB

Glasdegib, in combination with LDAC, was approved by the FDA in November 2018 for the frontline treatment of elderly (>75 yr) or unfit patients. Glasdegib is an oral inhibitor of the hedgehog signaling pathway [44, 45]. Recently, the aberrant activation of the hedgehog signaling pathway has been implicated in the maintenance and development of several malignancies including AML [46]. Glasdegib received FDA approval based on a phase II, randomized, open-label, multicenter study (NCT01546038), in which 88 and 44 patients (older than 75 yr or older than 55 yr with significant comorbidities) were randomized to glasdegib/LDAC and LDAC, respectively [47]. The results demonstrated that glasdegib/LDAC was superior to LDAC alone, indicating better survival (the median OS of 8.3 mo vs. 4.9 mo, P=0.0004) and a higher CR rate (17.0% vs. 2.3%, $P<0.05$) in the glasdegib/LDAC combination arm.

CONCLUSION AND DISCUSSION

Over the years, there has been a gradual paradigm shift from traditional medicine to personalized or precision medicine owing to the explosive growth in available genetic data [48]. Traditional or conventional medicine is characterized by empirical and mechanism-based treatments, targeting an entire population. On the contrary, precision medicine targets an individual patient based on the understanding of the unique molecular mechanisms of the patient [48, 49].

In the field of AML, there has been the growing understanding and discovery of leukemogenic pathways in the past years, and an innovative approach to AML treatment has "long" been expected. However, in the last 40 years, little has changed in the treatment of AML. Moreover, the majority of therapeutic advances in AML are associated with improved supportive care rather than the introduction of novel therapeutics.

Fortunately, with the introduction of numerous novel agents, we are now witnessing a new era in AML treatment [7]. Notably, 2017 was a memorable year in the history of AML treatment, marking the success of biomedical research efforts over the last several decades. The one of future challenges will be to incorporate and use these new therapeutics where they have the greatest impact – use alone or combine targeted agents with each other or with conventional chemotherapy [50].

Lastly, in Korea, we still have a long way to go, with limited access to these novel agents in clinical practice. Although these are not all-around, I hope that these new FDA approvals are no longer 'a pie in the sky' for Korean patients as well in a near future.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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