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REVIEW

New drugs approved for acute myeloid leukaemia in 2018

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Acute myeloid leukaemia (AML) is a haematopoietic stem cell disorder, that is characterized by the clonal expansion of myeloid blasts and suppression of normal haematopoiesis. The 3 + 7 regimen is the backbone of standard first-line induction therapy among young/fit patients. However, in elderly and/or unfit patients with newly diagnosed AML, who cannot receive intensive chemotherapy, low-dose cytarabine or hypomethylating agents (azacitidine or decitabine) are the treatment options, which generally cannot induce durable responses. Among young/fit patients, for high-risk disease in first remission, or in cases with relapsed/refractory AML, allogeneic stem cell transplantation should be performed when complete remission is achieved. However, since AML is primarily a disease of the elderly, neither intensive chemotherapy nor allogeneic stem cell transplantation can be generally tolerated in most cases. There is clearly a need for new treatment options in elderly and young/unfit patients who cannot receive intensive chemotherapy. The discovery of novel molecular genetic markers (e.g. FMS-like tyrosine kinase 3, isocitrate dehydrogenase 1 and 2) resulted in the development of new therapeutic options in AML. This review mainly focuses on 4 targeted therapy agents; glasdegib and venetoclax used in combination treatment with low-dose cytarabine or hypomethylating agents among newly diagnosed cases with AML; and ivosidenib and gilteritinib as monotherapy in the treatment of relapsed/refractory AML, which were all approved by the US Food and Drug Administration in 2018.

KEYWORDS
acute myeloid leukaemia, gilteritinib, glasdegib, ivosidenib, venetoclax

1 | INTRODUCTION

Acute myeloid leukaemia (AML) is characterized by the clonal expansion of myeloid blasts, and the median age of AML is 68 years.[1] AML is a very heterogeneous disease, and especially the somatic driver mutations are very important in the pathogenesis. Next generation sequencing technologies have provided the discovery of novel molecular genetic markers (e.g. FMS-like tyrosine kinase 3 [FLT3], isocitrate dehydrogenase [IDH]1, IDH2) in AML. These mutations then are identified as therapeutic targets for some novel drugs.[2] In elderly patients with AML and in those who are unfit for intensive treatment due to comorbidities, the treatment options are extremely limited and are often far from curative.[3] For young/fit patients, the 3 + 7 regimen is the backbone of standard induction therapy.[4] However, in elderly and/or unfit patients with newly diagnosed AML, who cannot receive intensive chemotherapy, low-dose cytarabine (LDAC) or hypomethylating agents (HMAs; azacitidine or decitabine) are the treatment options, which generally cannot induce durable responses.[3]

Among young/fit patients, for high-risk disease in first remission, or in cases with relapsed/refractory AML (RRAML), allogeneic stem cell transplantation should be performed when complete remission (CR) is achieved. However, since AML is primarily a disease of the elderly, neither intensive chemotherapy nor allogeneic stem cell transplantation can be generally tolerated in most cases. Kantarjian et al.[5] analysed 446 patients who were >70 years with AML, and results of the study indicated that the prognosis of most patients was poor with

intensive chemotherapy (8-week mortality >30%; median survival <6 months). If, RRAML is accompanied by particularly poor cytogenetic/molecular factors, the treatment response rates are low, and the overall survival (OS) is relatively short.[5,6]

Putting all these together, there is clearly a need for new treatment options in elderly and young/unfit patients who cannot receive intensive chemotherapy. There are some treatment options, which were recently approved and can also be used in these cases. In 2017, gemtuzumab ozogamicin, enasidenib and midostaurin were approved by the Food and Drug Administration (FDA). Gemtuzumab ozogamicin is a targeted therapy that is a humanized CD-33 directed monoclonal antibody–drug conjugate, and this drug received FDA approval for the treatment of adult patients with newly diagnosed CD33-positive RRAML.[7] Enasidenib is a small-molecule inhibitor of isocitrate IDH2, which was approved for the use in adult cases with RRAML and an IDH2 mutation.[8] Midostaurin is a tyrosine kinase inhibitor (TKI) that inhibits multiple receptors such as FLT3, and it was approved for the management of adult patients with newly diagnosed AML who are positive for FLT3, in combination with standard 3 + 7 induction regimen and cytarabine consolidation.[9]

This review mainly focuses on 4 agents: glasdegib and venetoclax used in combination treatment with LDAC or HMAs among newly diagnosed cases with AML[10,11]; and ivosidenib and gilteritinib as monotherapy in the treatment of RRAML,[12,13] which were all approved by the FDA in 2018. So far, these 4 agents are only approved in the USA.

2 | AGENTS APPROVED FOR PATIENTS WITH RRAML

2.1 | Ivosidenib

Ivosidenib (Tibsovo) is a small-molecule inhibitor of **IDH1**. Mutant IDH1 increases levels of 2-hydroxy-glutarate (2-HG) in leukaemic cells. 2-HG competitively inhibits α-ketoglutarate dependent enzymes which cause epigenetic alterations and impaired hematopoietic differentiation. Ivosidenib depresses 2-HG production and it provokes cell differentiation.[14,15]

IDH1 mutation is observed in approximately 6–16% of AML cases and is related to poor prognosis.[16,17] The IDH1 mutation status has to be confirmed in the blood or bone marrow at diagnosis. During relapse, cases without an initial IDH1 mutation must be retested.

In the study of DiNardo et al.,[15] which is a phase I, multicentre, open-label, dose escalation and dose-expansion study (NCT02074839), 179 patients with RRAML treated with ivosidenib (500 mg/d orally) have been reported to have CR + CR with incomplete haematological recovery (CRi) and overall response rates (ORR = CR + CRi + partial remission) of 30.2% and 39.1%, respectively (Table 1). Median time to first response and median duration of response were 1.9 and 6.5 months, respectively.

There were no grade ≥ 3 adverse events (AEs) observed with a frequency of ≥10%. The most common AEs were QT_c prolongation (7.8%) and differentiation syndrome (3.9%). The dose of ivosidenib has to be adjusted, when used concomitantly with strong CYP3A4 inhibitors.[12]

Ivosidenib has received its FDA approval for adult patients with RRAML with a susceptible IDH1 mutation detected by an FDA-approved assay.[12]

2.2 | Gilteritinib

Gilteritinib (Xospata) is a tyrosine kinase inhibitor (TKI) which inhibits multiple tyrosine kinases such as **FLT3**. This second generation FLT3-targeted TKI is more selective and more potent compared to midostaurin.[18]

The FLT3 mutation is seen in 30–40% of AML cases and is related to poor prognosis.[19] Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells expressing internal tandem duplication (ITD), tyrosine kinase domain mutations (TKD), FLT3-D835Y and FLT3-ITD-D835Y; induces apoptosis in leukaemia cells expressing FLT3-ITD. By contrast, like FLT3, AXL is a receptor tyrosine kinase, and the overexpression of AXL has been associated with poor prognosis in AML and resistance to standard chemotherapy. Gilteritinib is a dual FLT3/AXL inhibitor.[18,20]

A phase III, open-label, multicentre, randomized ADMIRAL study (NCT02421939) is still enrolling adult patients with RRAML harbouring FLT3 ITD, D835 or I836 mutation, and patients are randomized in 2:1 ratio to receive gilteritinib or salvage chemotherapy. The preliminary results were published in 138 patients treated with gilteritinib (120 mg per day orally).[21] After a median follow-up of 4.6 months, CR + CRi rates were reported as 21% in the gilteritinib arm (Table 1). The most common grade ≥ III AEs are shown in Table 1. Strong CYP3A4 inhibitors and inducers should be avoided in patients receiving gilteritinib treatment.[13]

The FDA granted an approval for gilteritinib in the treatment of adult patients who have RRAML with the positive FLT3 mutations, which were determined in blood or bone marrow with an FDA-approved test.[13]

3 | AGENTS APPROVED FOR PATIENTS WITH NEWLY DIAGNOSED AML

3.1 | Venetoclax

Venetoclax (Venclexta) is an oral **BCL-2** inhibitor, and BCL-2 mediates the survival of the tumour cell and is associated with chemotherapy resistance. Venetoclax binds directly to the BCL-2 protein and selectively inhibits BCL-2 by relocating the proapoptotic proteins and restoring apoptosis.[22,23]

A nonrandomized, open-label, multicentre, phase Ib-escalation and expansion study (NCT02203773) was conducted in 145 patients, who were age ≥ 65 years with treatment-naïve AML and ineligible for intensive chemotherapy.[24] Venetoclax was administered at 400, 800 or 1200 mg per day orally in combination with either decitabine (20 mg/m^2, days 1–5, intravenously) or azacitidine (75 mg/m^2, days 1–7, intravenously or subcutaneously). The rate of CR + CRi was 67%,

TABLE 1 New agents approved by the FDA in 2018 for the treatment of AML

Drug	Mechanism of action	Indication of FDA approval	Date of approval	Dose (treatment regimen)	Pivotal trial [ref no]	Phase	Primary endpoints	Secondary endpoints	Grade ≥ 3 adverse events*
Venetoclax	Bcl-2 inhibitor	Newly diagnosed AML in combination therapy	21 November 2018	Day 1: 100 mg Day 2: 200 mg Day 3: 400 mg If with AZA or decitabine, Day4 and beyond 400 mg If with low dose cytarabine, Day4 and beyond 600 mg	NCT02203773[24] NCT02287233[25]	Ib Ib/II	Median OS 17.5 mo (all patients; venetoclax 400 mg + HMA cohort was 73%) median OS 10.1 mo (all patients)	CR + CRi 67% CR + CRi 54% (without prior HMA exposure 62%)	Anaemia Fatigue Febrile neutropenia Hypertension Hyperuricaemia Hypokalaemia Hypophosphataemia Leucopenia Lymphocytopenia Neutropenia Pneumonia Sepsis Thrombocytopenia
Ivosidenib	IDH-1 inhibitor	Relapsed/ refractory AML	20 July 2018	500 mg once daily	NCT02074839[15]	I	CR + CRi 30.2% ORR 39.1%	Median time to first response 1.9 mo Median duration of response 6.5 mo	Differentiation syndrome** QT_c prolongation**
Gilteritinib	FLT-3/AXL inhibitor	Relapsed/ refractory AML	28 November 2018	120 mg once daily	ADMIRAL NCT02421939[21]	III	CR + CRi 21%	31.1% became transfusion independent	Elevated transaminases Dyspnoea Pneumonia Sepsis Hypophosphataemia Hyponatraemia
Glasdegib	Hedgehog pathway inhibitor	Newly diagnosed AML in combination therapy	21 November 2018	100 mg once daily	NCT01546038[27]	II	Median OS 8.8 vs. 4.9 mo (HR: 0.51; 80% CI, 0.39–0.67, $P = .0004$)	CR rates 17% vs 2.3% against cytarabine alone ($P < .05$)	Anaemia Fatigue Febrile neutropenia Pneumonia Thrombocytopenia

AML, acute myeloid leukaemia; AZA, azacitidine; BCL-2, B-cell leukaemia/lymphoma-2; CI, confidence interval; CR, complete remission; CRi, CR with incomplete haematological recovery; FDA, Food and Drug Administration; FLT-3, FMS-like tyrosine kinase 3; HMA, hypomethylating agent; HR, hazard ratio; IDH-1, isocitrate dehydrogenase 1; mo, months; ORR, overall response rate; OS, overall survival).

*grade ≥ III AEs observed in a frequency of ≥10%.

**these were the most common grade ≥ III AEs; however, they were observed in <10% of the cases.

and the median OS 17.5 months (for all venetoclax doses; Table 1). The rate of CR + CRi for venetoclax 400 mg plus HMA cohort was 73%. As tumour lysis syndrome can be a significant problem in patients receiving venetoclax, this complication was not observed in this study, but patients with a leucocyte count >25 × 10^9/L were excluded from the trial.

In another open-label, multicentre, phase Ib/II study (NCT02287233), 82 treatment-naïve AML patients, who were age ≥ 60 years and ineligible for intensive chemotherapy (including patients with a history of using an HMA for a previously known haematological disease) received a combination of LDAC (20 mg/m^2, days 1–10, subcutaneously) and venetoclax (dose increased over 4 days to target venetoclax dose, 600 mg; Table 1).[25] CR + CRi rate was 54%, with a median OS of 10.1 months. Among patients without prior HMA exposure, rate of CR + CRi was 62% (Table 1).

Grade ≥ III AEs reported in ≥10% of patients are shown in Table 1. [24,25] If given together with simultaneous strong or moderate CYP3A inhibitors or P-glycoprotein (P-gp) inhibitors, dose adjustment is required for venetoclax.[11]

Following these results, venetoclax was approved by FDA in combination with HMAs or LDAC for the treatment of newly diagnosed AML in adults who are age ≥ 75 years or who have comorbidities that preclude use of intensive induction chemotherapy.[11] The dose of venetoclax varies depending on the chemotherapy agent given to the concomitant. In all combinations, venetoclax dose is increased 2 times day by day during first 3 days. On day 4 and beyond, if combined with HMAs, venetoclax dose is maintained 400 mg; however, if combined with LDAC, venetoclax dose is 600 mg (Table 1).

3.2 | Glasdegib

Glasdegib (Daurismo) is a selective oral inhibitor of Hedgehog pathway and it inhibits Hedgehog signalling through binding to **Smoothened**, a transmembrane protein, then prevents the activation of Smoothened-mediated downstream Hedgehog targets.[26]

A phase II, randomized, open-label, multicentre study (NCT01546038) was conducted among 132 high-risk myelodysplastic syndrome and newly diagnosed AML patients who were not suitable for intensive chemotherapy.[27] Patients were randomized in 2:1 fashion as LDAC only (*n* = 44) *vs* glasdegib plus LDAC (*n* = 88). In the combination arm, the median OS was 8.8 months *vs* 4.9 months (hazard ratio: 0.51; 80% confidence interval, 0.39–0.67, *P* = .0004) and the rates of CR were superior in the combination arm (17 *vs* 2.3%, *P* < .05; Table 1).

Grade ≥ 3 AEs observed with a frequency ≥ 10% in the study of Cortes et al.[27] are shown in Table 1. In addition to that, in patients receiving glasdegib, strong CYP3A4 inhibitors and inducers should be avoided.[10]

Glasdegib received FDA approval in the form of a single dose 100 mg/d with LDAC 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle in adults who are age ≥ 75 years or who have comorbidities that preclude use of intensive induction chemotherapy in the treatment of newly diagnosed AML.[10]

4 | CONCLUSIONS

Elderly and young/unfit AML patients who cannot receive intensive chemotherapy and patients with RRAML are the most difficult groups to manage. Treatment response, drug tolerability and survival of these patients are generally low.

Together with others, the new agents that were approved by FDA in 2018 are promising with ease of use (orally), rapid treatment responses, and ORRs (particularly in patients with poor risk factors) with generally acceptable toxicity profiles. The combination of these new agents with traditionally low-intensity therapies (LDAC or HMAs) could be reasonable approaches among these patient groups with relatively limited treatment options. With promising results and early favourable outcomes with manageable toxicity profiles, these novel agents may also result in financial toxicity and cost-effectivity should not be ignored while choosing the treatment.

Although not approved in those settings/combinations yet, there are many ongoing clinical trials with these targeted therapies in patients with AML,[28-31] and most probably those FDA-approved drugs will in the future be used in combinations with each other, and with low intensity and intensive chemotherapies.

To conclude, these 4 drugs showed some promising results initially regarding both efficacy and tolerability; however, most of these drugs were approved following phase I/II trials, and for our point of view, these results need to be further confirmed by phase III studies.

Nomenclature of target and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY,[32] and are permanently achieved in the Concise Guide to PHARMACOLOGY 2017/2018.[32-35]

COMPETING INTERESTS

There are no competing interests to declare.

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