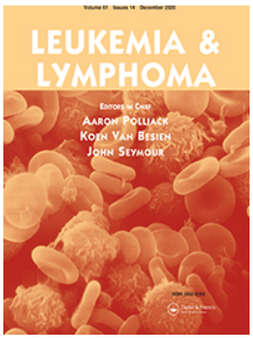

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REVIEW

Selection and management of older patients with acute myeloid leukemia treated with glasdegib plus low-dose cytarabine: expert panel review

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ABSTRACT

Glasdegib, in combination with low-dose cytarabine (LDAC), is the first smoothened inhibitor approved for treatment of acute myeloid leukemia. Glasdegib plus LDAC is indicated for patients in whom therapy options are limited, e.g. older patients and those ineligible for intensive chemotherapy due to preexisting comorbidities. This review summarizes the recommendations of a panel of hemato-oncologists regarding the selection of patients best suited for treatment with glasdegib plus LDAC and the management during therapy with this combination. The panel considered the impact of concomitant medications and comorbidities during treatment with glasdegib plus LDAC, and discussed common adverse events (AEs) associated with glasdegib plus LDAC. Management strategies for AEs discussed by the panel included dose modifications, supportive care therapies, and prophylactic treatments. Finally, the panel highlighted the importance of patient communication and education regarding the possible AEs that may occur during treatment.

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Acute myeloid leukemia; adverse events; comorbidities; glasdegib; low-dose cytarabine; older patients

Introduction

Acute myeloid leukemia (AML) is a complex heterogeneous disease [1–4]. Intensive induction/consolidation therapy gives the best chance for cure, but not all patients are candidates [2,5–7]. Selection is mostly subjective assessment based on clinical observations, with no universally accepted or validated tools to determine eligibility. Characteristics commonly considered in clinical practice include age, Eastern Cooperative Oncology Group performance status (ECOG PS), cytogenetic risk, and comorbidities [2,8–17]. In patients aged ≥60, the following variables were associated with complete remission (CR) or early death: age, *de novo* AML, laboratory parameters, and comorbidities [18].

Evidence varies regarding intensive chemotherapy (IC) in older patients with AML [13,19–29]. Improved outcomes and survival benefits were reported in patients aged ≥60 who received IC regimens versus those who received no treatment; in some reports, this was irrespective of comorbidity burden [19–24,28,29]. Others indicated that, despite high rates of CR, only a carefully selected subset of older patients with AML can be considered for IC [13,25–27].

Traditionally, patients ineligible for IC have been treated with low-dose cytarabine (LDAC) or hypomethylating agents (HMAs) [2,5–7]. However, a clearer understanding of AML pathogenesis has led to new options, with treatment selection based on patient and disease characteristics. Although decisions are sometimes steered by objective criteria (e.g. FMS-like tyrosine kinase 3 (FLT3) inhibitor for patients with *FLT3* mutations), guidance is needed regarding patient selection and therapy management. A meeting of expert hemato-oncologists was held to define the use of glasdegib plus LDAC in treatment of older patients with AML, in particular, to define those best suited for this therapy and provide guidance on managing therapy-related adverse events (AEs). The

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Supplemental data for this article can be accessed here.

recommendations of this expert panel are described here. An associated manuscript plain language summary can be found in Supplementary Materials.

Setting and methods

On 12 April 2019 in London, UK, nine hemato-oncologists from centers across Europe, Canada, and the USA participated in an expert panel. All had extensive experience in treating AML and the use of glasdegib plus LDAC, glasdegib as monotherapy, and/or glasdegib in combination with other therapies in patients with AML.

The experts discussed their clinical experience with standard and experimental treatments for AML, patient characteristics that influence their decisions, and AE management with glasdegib plus LDAC. These discussions were captured and formed the foundation of this manuscript that underwent critical review by all experts.

Approved treatments and related clinical trial experience

A number of therapies are approved by the US Food and Drug Administration (FDA) and/or European Medicines Agency (EMA) for treatment of patients with AML ineligible for IC (Table 1 and Figure 1). Decision-making criteria regarding patient eligibility for IC are both subjective (e.g. inclusion/exclusion criteria, clinical trial characteristic) and objective (e.g. label indication, age, mutations) (Tables 2 and 3).

Standard treatments

Decitabine and azacitidine are standard-of-care therapies for older patients and those ineligible for IC; LDAC is another available alternative treatment [49]. In a randomized study, LDAC 20 mg twice daily (BID) was compared with hydroxyurea in patients primarily aged ≥60 ineligible for chemotherapy. Patients aged <70 were required to have additional comorbidities that precluded chemotherapy [43]. Median age was 74 (range: 51–90). CR was achieved in 18% (LDAC) and 1% (hydroxyurea) and overall survival (OS) was better with LDAC ($p = .0009$). Common all-causality AEs during course 1 were cardiac (10% and 11%), nausea (6% each), and diarrhea (4% and 10%) with LDAC and hydroxyurea, respectively [43].

A phase 3 study evaluated decitabine (20 mg/m^2 intravenous (IV) on a five-day schedule) versus treatment choice in patients aged ≥65, ECOG PS 0–2, and poor/intermediate-risk cytogenetics [47]. Median OS (mOS) and CR rates were 7.7 months and 15.7% (decitabine) and 5.0 months and 7.4% (treatment choice). Common all-causality AEs (grades 3–4) with decitabine and treatment choice, respectively, were thrombocytopenia (40% and 32%), anemia (34% and 25%), febrile neutropenia (32% and 22%), and neutropenia with decitabine (32%) [47].

In a phase 3 study, patients aged ≥65 with poor/intermediate-risk cytogenetics received azacitidine (75 mg/m^2/day) or conventional care regimens [48]. mOS and CR were 10.4 months and 21.9% (azacitidine) and 6.5 months and 21.9% (conventional care). Common all-causality AEs for azacitidine, LDAC, and IC, respectively, were febrile neutropenia (28%, 30.1%, and 31%), neutropenia (26.3%, 24.8%, and 33.3%), and thrombocytopenia (23.7%, 27.5%, and 21.4%) [48].

Targeted therapies

In recent years, a number of targeted therapies have become available, or are in clinical development, for patients ineligible for IC.

The smoothened inhibitor (SMOi) glasdegib 100 mg once daily (QD) is FDA-approved in combination with LDAC 20 mg BID for patients with AML aged ≥75 or ineligible for induction IC [35]. Glasdegib plus LDAC has been granted initial authorization by the EMA to treat newly diagnosed *de novo* or secondary AML (sAML) in adult patients who are not candidates for standard induction chemotherapy AML [36]. Approval of glasdegib was based on the results from the pivotal phase 2 BRIGHT MDS&AML 1003 trial [40,50–52] (Table 4). In BRIGHT AML 1003, survival probability for glasdegib plus LDAC versus LDAC alone, respectively, was 39.4% and 8.4% at 1 year, and 19.0% and 2.8% at 2 years [50]. In a quality-adjusted time without symptoms of disease progression or toxicities (Q-TWiST) analysis of BRIGHT AML 1003, patients receiving glasdegib plus LDAC had longer time in relatively 'good' health compared with those receiving LDAC alone [53]. OS was similar, and CR rate was slightly lower, for LDAC alone in the BRIGHT MDS&AML 1003 study compared with the previous LDAC study, indicating that the LDAC control arm in BRIGHT MDS&AML 1003 is representative of the AML population [43]. In BRIGHT MDS&AML 1012, 17% (MDS) and 20% (AML) achieved CR and mOS was not reached with glasdegib (100 mg QD) plus azacitidine (75 mg/m^2/day) in either population [54,55]. Glasdegib 100 mg QD is also being investigated in combination with decitabine 20 mg/m^2 IV on a 5- or 10-day schedule in older patients with poor-risk AML (NCT04051996). Several other clinical

Table 1. Summary of agents approved for treatment of patients with AML ineligible for intensive chemotherapy.

Product	Mechanism of action	FDA approval status in AML	Approved dosage	EMA approval status in AML	Approved dosage
Azacitidine [30,31]	Hypomethylating agent	Indicated for MDS, including refractory anemia with excess blasts in transformation (i.e. 20–30% blasts), which is now classified as AML per contemporary classification systems	75 mg/m^2 SC or IV daily for 7 days (28-day cycle). Increase to 100 mg/m^2 after 2 cycles if no beneficial effect or toxicity observed	Indicated for intermediate-II and high-risk MDS according to the IPSS, AML with 20–30% blasts and multilineage dysplasia, according to WHO classification, and AML with >30% marrow blasts according to WHO classification	75 mg/m^2 SC or IV daily for 7 days (28-day cycle)
Cytarabine [2,32]	Nucleoside metabolic inhibitor	Indicated in combination with other approved anticancer drugs for induction in acute non-lymphocytic leukemia of adults and children	100–200 mg/m^2/day cytarabine by continuous IV for 7 days	Historical use	100–200 mg/m^2/day cytarabine by continuous IV for 7 days
Decitabine [33,34]	Hypomethylating agent	Indicated for adult patients with MDS, including previously treated and untreated, *de novo* and secondary MDS of all French/American/British subtypes and intermediate-I, intermediate-II, and high-risk IPSS groups	*4-week cycle:* 20 mg/m^2 IV over 60 min for 5 days *6-week cycle:* 15 mg/m^2 continuous IV over 3 h, repeated every 8 h, for 3 days	Patients with newly diagnosed *de novo* or secondary AML, according to WHO classification, who are not candidates for standard induction chemotherapy	20 mg/m^2 IV over 60 min for 5 days (4-week cycle)
Glasdegib [35,36]	SMO inhibitor	In combination with LDAC for adult patients with AML aged ≥75 or who have comorbidities that preclude use of intensive induction chemotherapy	100 mg/day PO	Initial authorization in combination with LDAC for newly diagnosed *de novo* or secondary AML in adult patients who are not candidates for standard induction chemotherapy	To be confirmed
Ivosidenib [37,38]	IDH1 inhibitor	Indicated for treatment of AML with a susceptible *IDH1* mutation in adult patients with newly diagnosed AML who are aged ≥75 or who have comorbidities that preclude use of intensive induction chemotherapy, or adult patients with R/R AML	500 mg/day PO	Granted orphan designation for treatment of AML	Not applicable
Venetoclax [39]	BCL-2 inhibitor	In combination with azacitidine or decitabine or LDAC for newly diagnosed AML in adults who are aged ≥75, or who have comorbidities that preclude use of intensive induction chemotherapy	100 mg (day 1), 200 mg (day 2), 400 mg (day 3), 400 mg (days 4+; in combination with azacitidine or decitabine) or 600 mg (days 4+; in combination with low-dose cytarabine)	Not yet approved for AML	Not applicable

AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; EMA: European Medicines Agency; FDA: US Food and Drug Administration; IDH: isocitrate dehydrogenase; IPSS: International Prognostic Scoring System; IV: intravenously; LDAC: low-dose cytarabine; MDS: myelodysplastic syndrome; PO: orally; R/R: relapsed or refractory; SC: subcutaneously; SMO: smoothened; WHO: World Health Organization.
Details correct as of 10 July 2020.

trials of glasdegib as monotherapy or combination therapy in AML have completed or are underway, in particular, a phase 3 trial of glasdegib/placebo plus 7 + 3 or glasdegib/placebo plus azacitidine in untreated AML (NCT03416179/BRIGHT AML 1019), and a number of phase 2 trials in various patient populations with AML (NCT03390296, NCT03226418, NCT01841333), are ongoing.

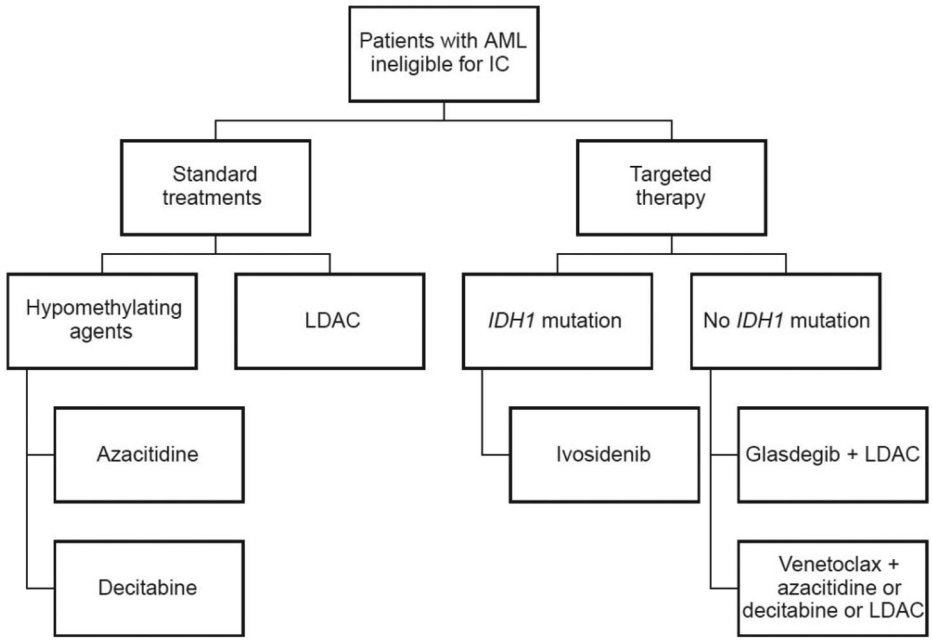

Figure 1. Agents approved for treatment of newly diagnosed patients with AML ineligible for intensive chemotherapy. AML: acute myeloid leukemia; IC: intensive chemotherapy; IDH: isocitrate dehydrogenase; LDAC: low-dose cytarabine.

The BCL-2 inhibitor venetoclax plus HMAs or LDAC is FDA-approved for treatment of newly diagnosed AML in patients aged ≥75 or ineligible for induction IC [39]. A phase 1B study evaluated venetoclax (400, 800, or 1200 mg QD) plus HMAs in patients aged ≥65 ineligible for standard induction chemotherapy due to age ≥75, comorbidities (e.g. cardiac disease, prior anthracycline use, sAML), or high probability of treatment-related mortality [42]. mOS was 17.5 months, and 37% achieved CR. Common all-causality AEs (grades 3–4) were febrile neutropenia (43%), decreased white blood cell count (31%), and anemia (25%) [42]. Neutropenia occurred among 40% of patients who experienced AEs leading to venetoclax dose interruption. Additionally, 33% of patients with neutropenia delayed cycle 2 treatment to allow absolute neutrophil count recovery [42]. Another phase 1B/2 study assessed venetoclax 600 mg QD plus LDAC 20 mg/m^2/day in patients aged ≥60 ineligible for IC due to comorbidity or other factors [41]: ECOG PS 0–2 was required for patients aged ≥75; ECOG PS 0–3 for patients aged 60–74; an additional comorbidity for those with ECOG PS 0–1 [41]. mOS was 10.1 months, and 26% achieved CR. Dose interruptions due to AEs occurred in 55% of patients and included delayed neutrophil ($n=$ 8) and platelet recovery ($n=$ 10). Dose reductions due to AEs (7%) were mostly due to thrombocytopenia. Common all-causality AEs were nausea (70%), diarrhea (49%), and hypokalemia (48%) [41]. Interim results from a phase 3 study of venetoclax plus LDAC versus LDAC alone, respectively, reported mOS of 7.2 and 4.1 months and CR of 27.3% and 7.4%, a difference that was not statistically significant [56].

Recurrent *IDH* mutations, found in ≈20% of AML cases, are associated with older age, intermediate-risk cytogenetics, and other mutations [6,57,58]. The IDH1 inhibitor ivosidenib is also approved for newly diagnosed patients who are older or ineligible for IC, and patients with R/R disease [37,38]. A phase 1 study investigated ivosidenib in patients aged ≥18 with *IDH1*-mutated AML; the trial included a cohort of patients who were aged ≥75 or who were ineligible for IC due to comorbidities [37,38,45]. mOS in the primary population was 8.8 months and 21.6% achieved CR [45]. Common all-causality AEs were diarrhea (33.3%), leukocytosis (30.2%), and nausea (29.5%) [45].

The antibody–drug conjugate gemtuzumab ozogamicin (GO) and the IDH2 inhibitor enasidenib are not yet approved by the FDA and EMA for newly diagnosed patients with AML who are ineligible for IC [59–62]; however, they have been investigated in these patients in clinical trials. The phase 3 EORTC-GIMEMA study evaluated GO (6 mg/m^2 on day 1, and 3 mg/m^2 on day 8) versus best supportive care in elderly patients ineligible for IC [44]. Patients were aged >75 or 61–75 with a World Health Organization (WHO) performance score >2 or otherwise ineligible for IC. mOS was 4.9 (GO) and 3.6 (best supportive care) months; 8.1% of patients receiving GO achieved CR. Common all-causality non-hematologic AEs with GO and best supportive care, respectively, were liver

Table 2. Summary of eligibility criteria in key clinical trials in patients with AML who are ineligible for intensive treatment.

Study design	Treatments	Age	Diagnosis	ECOG PS and cytogenetic risk	Other
Patients ineligible for IC					
BRIGHT MDS&AML 1003: Open-label, multicenter phase 2 study [40]	Patients were randomized 2:1 to: glasdegib 100 mg QD + LDAC 20 mg BID ($N = 88$) or LDAC 20 mg BID alone ($N = 44$)	≥55	Newly diagnosed Previously untreated AML or high-risk MDS	See other Known cytogenetic profile	Considered not suitable for IC, ≥1 of the following criteria: Age: ≥75 Serum creatinine: >1.3 mg/dL Severe cardiac disease ECOG PS = 2 ECOG PS = 0 or 1+≥1 other criteria listed above
Open-label, multicenter, multinational phase 1B/2 study [41]	82 patients received venetoclax 600 mg QD + LDAC 20 mg/m^2/day	≥60	Previously untreated AML Patients with secondary AML or prior treatment with HMAs for MDS were permitted	ECOG PS = 0–2 if aged ≥75 ECOG PS = 0–3 if aged 60–74 (if ECOG PS = 0–1, another comorbidity was required)	Ineligible for IC due to comorbidity or other factors Life expectancy >12 weeks White blood cells: $\leq 25 \times 10^9$/L Cardiovascular disability status of NYHA class ≤ II
Multicenter, phase 1B dose-escalation and expansion study [42]	145 patients received venetoclax at 400, 800, or 1200 mg/day + decitabine 20 mg/m^2 or azacitidine 75 mg/m^2	≥65	Previously untreated AML	ECOG PS = 0–2	Adequate renal and hepatic function White blood cell count of $\leq 25 \times 10^9$/L Ineligible for standard induction chemotherapy due to comorbidities, such as: Age: >75 Cardiac disease Prior anthracycline use Secondary AML High probability of treatment-related mortality
Prospective randomized study [43]	Patients were randomized to LDAC 20 mg BID ($N = 103$) or hydroxyurea ($N = 99$)	≥60	*De novo* or secondary AML or high-risk MDS	Not specified	No specific criteria used to define patients considered not fit for intensive treatment, except: Patients aged <70 should have a documented comorbidity that precluded chemotherapy Patients who entered the non-intensive approach were significantly older, had a poorer performance score, had more secondary disease, and had more heart disease and documented comorbid conditions
EORTC-GIMEMA AML-19: Open-label, phase 3 study [44]	Patients were randomized 1:1 to a single induction course of GO (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8; $N = 118$) or best supportive care ($N = 119$)	>75	Previously untreated AML (*de novo* or secondary to myelodysplasia) and who were deemed ineligible for IC	See other	Age: 61–75 with a WHO performance score >2 or who were unwilling to receive standard chemotherapy Serum creatinine and liver function test results (bilirubin and transaminases): ≤1.5 × ULN White blood cell count: $<30 \times 10^9$/L

(*continued*)

Table 2. Continued.

Study design	Treatments	Age	Diagnosis	ECOG PS and cytogenetic risk	Other
Phase 1 multicenter, open-label, dose-escalation and dose-expansion study [45]	258 patients received ivosidenib 500 mg/day	≥18	R/R *IDH1*-mutated AML	ECOG PS = 0–2	Included a cohort of patients who were ≥75 or who had comorbidities that precluded the use of IC based on ≥1 of the following criteria: ECOG PS ≥2 Severe cardiac or pulmonary disease hepatic impairment with bilirubin >1.5 × ULN Creatinine clearance <45 mL/min
Multicenter, open-label, single-arm study [46]	39 patients received enasidenib 50–650 mg/day	≥18	Previously untreated *IDH2*-mutated AML	ECOG PS = 0–2	Not candidates for standard AML treatments
Older patients					
Multicenter, randomized, open-label, phase 3 study [47]	Patients were randomized 1:1 to: decitabine 20 mg/m^2/day (N = 242) or treatment choice (N = 243; supportive care or cytarabine 20 mg/m^2/day)	≥65	Previously untreated *de novo* or secondary AML	ECOG PS = 0–2 Poor- or intermediate-risk cytogenetics	>30% bone marrow blasts White blood cell count: ≤15/mm Not considered eligible for HSCT
Multicenter, randomized, open-label, phase 3 study [48]	Patients were randomized 1:1 to azacitidine 75 mg/m^2/day (N = 241) or conventional care regimens (N = 247; standard induction chemotherapy, LDAC, or supportive care only)	≥65	*De novo* or secondary AML	ECOG PS = 0–2 Poor- or intermediate-risk cytogenetics	White blood cell count: ≤40,000/mm Bilirubin: ≤1.5 × ULN AST/ALT: ≤2.5 × ULN Creatinine clearance: ≥40 mL/min Life expectancy ≥12 weeks Exclusion criteria included: unstable angina or NYHA class III/IV congestive heart failure, inaspirable bone marrow, comorbidities, or organ dysfunction

7 + 3: cytarabine 100 mg/m^2 IV for 7 days by continuous infusion, and daunorubicin 60 mg/m^2 for 3 days; ALT: alanine transaminase; AML: acute myeloid leukemia; AST: aspartate transaminase; BID: twice daily; CMML: chronic myelomonocytic leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; GFR: glomerular filtration rate; GO: gemtuzumab ozogamicin; HMA: hypomethylating agent; HSCT: hematopoietic stem cell transplant; IC: intensive chemotherapy; IDH: isocitrate dehydrogenase; IV: intravenous; LDAC: low-dose cytarabine; LVEF: left ventricular ejection fraction; MDS: myelodysplastic syndromes; NYHA: New York Heart Association; QD: once daily; QTcF: QT interval corrected for heart rate using Fridericia's formula; R/R: relapsed or refractory; ULN: upper limit of normal; WHO: World Health Organization.

(51.3% and 45.6%), fatigue (45.9% and 60.5%), and infection (44.1% and 42.1%) [44]. In patients aged ≥18 with previously untreated *IDH2*-mutated AML ineligible for standard treatments (criteria not specified; at the discretion of the investigator), mOS was 11.3 months and 18% achieved CR with enasidenib [46]. Common all-causality AEs were fatigue (44%), decreased appetite (41%), nausea (38%), and constipation (38%) [46].

Summary

Although similarities were observed across key clinical studies (comorbidities were an important criterion for determining ineligibility for IC; older patients tended to present with intermediate or adverse cytogenetic risk at baseline), there were large differences in inclusion/exclusion criteria and definitions for ineligibility for chemotherapy (where this was defined). Therefore, baseline characteristics varied greatly across key studies. This heterogeneity in patient populations makes cross-study comparisons inadequate and inadvisable as a guide for treatment selection in older patients with AML.

Considerations for glasdegib treatment selection

Dysregulation of the Hedgehog signaling pathway, and its component, SMO, play an important role in

Table 3. Summary of baseline characteristics in key clinical trials in patients with AML who are ineligible for intensive treatment.

Treatment	Median (range) age, years	ECOG PS	Cytogenetic risk	AML diagnosis	Prior treatment details	Mutations
Patients ineligible for IC						
Glasdegib 100 mg QD + LDAC 20 mg BID or LDAC 20 mg BID alone [40]	Glasdegib + LDAC: 77 (63–92) LDAC alone: 75 (58–83)	For glasdegib + LDAC and LDAC alone, respectively: 0: 12.5% and 6.8% 1: 33.0% and 40.9% 2: 53.4% and 52.3% Not reported: 1.1% and 0%	For glasdegib + LDAC and LDAC alone, respectively: Good/intermediate risk: 59.1% and 56.8% Poor risk: 40.9% and 43.2%	For glasdegib + LDAC and LDAC alone, respectively: AML: 88.6% and 86.4% MDS: 11.4% and 13.6%	Prior therapy with MDS drug for glasdegib + LDAC and LDAC alone, respectively: Azacitidine: 14.8% and 18.2% Decitabine: 2.3% and 2.3%	Genes mutated in ≥10% of patients for glasdegib + LDAC and LDAC alone, respectively: *CEBPA*: 13.8% and 12.0% *DNMT3A*: 25.9% and 24.0% *IDH1*: 13.8% and 8.0% *IDH2*: 19.0% and 16.0% *RUNX1*: 43.1% and 24.0% *TET2*: 24.1% and 36.0%
Venetoclax 600 mg QD + LDAC 20 mg/m^2/day [41]	74 (63–90)	0: 15% 1: 56% 2: 28% 3: 1%	Intermediate risk: 60% Poor risk: 32% No mitosis: 8%	*De novo*: 51% Secondary: 49%	Prior HMA treatment: 29%	*TP53*: 14% *FLT3*: 23% *IDH1/2*: 25% *NPM1*: 13%
Venetoclax at 400, 800, or 1200 mg/day + decitabine 20 mg/m^2 or azacitidine 75 mg/m^2 [42]	74 (65–86)	0: 22% 1: 62% 2: 16%	Intermediate risk: 51% Poor risk: 49%	*De novo*: 75% Secondary: 25%	Prior hydroxyurea: 12%	*FLT3*: 12% *IDH1/IDH2*: 24% *NPM1*: 16% *TP53*: 25%
LDAC 20 mg BID or hydroxyurea [43]	Age ≥75: LDAC: 49% Hydroxyurea: 48%	Performance score for LDAC and hydroxyurea, respectively: 0: 28% and 26% 1: 43% and 44% 2: 19% and 16% 3: 12% each 4: 1% each	For LDAC and hydroxyurea, respectively: Favorable risk: 2% and 1% Intermediate risk: 54% and 52% Adverse risk: 17% and 24% Unknown: 30% and 22%	For LDAC and hydroxyurea, respectively: *De novo*: 61% and 60% Secondary: 28% and 25% MDS: 14% and 14%	N/A	N/A
GO (6 mg/m^2 or best supportive care [44]	GO: 77 (62–88) Best supportive care: 77 (66–88)	WHO performance score for GO and best supportive care, respectively: 0–1: 64.4% and 64.7% 2: 28.8% and 27.7% >2: 6.8% and 7.6%	For GO and best supportive care, respectively: Favorable/intermediate risk: 50.0% and 37.8% Adverse risk: 28.0% and 26.9% Unknown risk: 22.0% and 35.3%	For GO and best supportive care, respectively: *De novo*: 66.9% and 71.4% Secondary: 33.1% and 28.6%	N/A	For GO and best supportive care, respectively: *CD33* <20: 8.5% and 11.8% *CD33* 20–80: 49.1% and 48.7% *CD33* >80: 40.7% and 39.5% Unknown: 1.7% and 0%
Ivosidenib 500 mg/day [45]	Primary population: 67 (18–87) R/R AML population: 67 (18–87)	N/A	For the primary and R/R AML populations, respectively: Favorable risk: 0% each Intermediate risk: 53% and 59% Poor risk: 30% and 28% Unknown/missing: 17% and 13%	For the primary and R/R AML populations, respectively: Primary AML: 66% and 67% Secondary AML: 34% and 33%	Prior therapy and response to prior therapy for the primary and R/R AML populations, respectively: IC: 74% and 71% Non-IC: 66% and 64% Investigational therapy: 30% and 31% Relapse after transplantation: 29% and 24% Second or later relapse:	For the primary and R/R AML populations, respectively: *FLT3*: 8% and 6% *NPM1*: 20% and 26% *CEBPA*: 3% and 2%

(*continued*)

Table 3. Continued.

Treatment	Median (range) age, years	ECOG PS	Cytogenetic risk	AML diagnosis	Prior treatment details	Mutations
					16% and 15% Disease that was refractory to initial induction Reinduction therapy: 69% and 59% Relapse within 1 year after initial therapy: 10% and 9%	
Enasidenib 50–650 mg/day [46]	77 (58–87)	0: 31% 1: 46% 2: 23%	Intermediate risk: 49% Poor risk: 26% Missing: 23%	Myelodysplasia-related changes: 36% Recurrent genetic abnormalities: 5% Therapy-related myeloid neoplasms: 5% Not otherwise specified: 51% Missing: 3%	N/A	*IDH2* mutant allele: R140: 67% R172: 31% Other/missing: 3% Genes mutated in $\geq$10% of patients: *SRSF2*: 53% *ASXL1*: 50% *STAG2*: 35% *RUNX1*: 29% *DNMT3A*: 24% *TET2*: 15% *NRAS*: 12%
Older patients						
Decitabine 20 mg/m^2/day or treatment choice (supportive care or cytarabine 20 mg/m^2/day) [47]	Decitabine: 73 (64–89) Treatment choice: 73 (64–91)	For decitabine and treatment choice, respectively: 0 or 1: 76.0% and 75.3% 2: 24.0% and 24.7%	For decitabine and treatment choice, respectively: Intermediate risk: 63.1% and 63.6% Poor risk: 36.1% and 36.0%	For decitabine and treatment choice, respectively: *De novo*: 64.0% and 64.6% Secondary: 36.0% and 34.6%	N/A	N/A
Azacitidine 75 mg/m^2/day or conventional care regimens (standard induction chemotherapy, LDAC, or supportive care only) [48]	Azacitidine: 75 (64–91) Conventional care regimens: 75 (65–89)	For azacitidine and conventional care regimens, respectively: 0 or 1: 77.2% and 76.8% 2: 22.8% and 23.2%	For azacitidine and conventional care regimens, respectively: Intermediate risk: 64.3% and 64.5% Poor risk: 35.3% and 34.4%	For azacitidine and conventional care regimens, respectively: AML, not otherwise specified: 63.5% and 57.9% AML with myelodysplasia-related changes: 31.1% and 33.6% AML with therapy-related myeloid neoplasms: 3.3% and 4.9% AML with recurrent genetic abnormalities: 2.1% and 3.6%	N/A	N/A

7 + 3: cytarabine 100 mg/m^2 IV for 7 days by continuous infusion, and daunorubicin 60 mg/m^2 for 3 days; AML: acute myeloid leukemia; BID: twice daily; CMML: chronic myelomonocytic leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; GO: gemtuzumab ozogamicin; HMA: hypomethylating agent; HSCT: hematopoietic stem cell transplant; IC: intensive chemotherapy; LDAC: low-dose cytarabine; MDS: myelodysplastic syndromes; N/A: not available; QD: once daily; R/R: relapsed or refractory; SD: standard deviation; WHO: World Health Organization.

Table 4. Summary of results from patients ineligible for IC in BRIGHT MDS&AML 1003 (including unpublished data) [40,50–52].

Parameter	Glasdegib plus LDAC	LDAC alone
BRIGHT MDS&AML 1003 population – data from [40], except where indicated	(*N* = 88)	(*N* = 44)
Patient characteristics, %		
Age >75	60.2	54.5
Comorbidities (unpublished data)		
Severe cardiac disease	65.9	47.7
Serum creatinine >1.3 mg/dL	21.6	11.4
Concomitant medications (unpublished data)		
Most common, *n*		
Allopurinol	54	27
Paracetamol	45	17
Furosemide	43	19
CYP3A4 inhibitors, *n*		
Ciprofloxacin/ciprofloxacin hydrochloride	31	9
Fluconazole[a]	24	14
Voriconazole	15	3
Posaconazole	13	3
Diltiazem/diltiazem hydrochloride	4	0
Itraconazole	3	3
Clarithromycin	2	3
Ketoconazole	1	0
Amiodarone/amiodarone hydrochloride	1	2
Verapamil/verapamil hydrochloride	1	1
Erythromycin	1	0
CYP3A4 inducers, *n*		
Dexamethasone/dexamethasone sodium phosphate	7	0
Carbamazepine	1	0
Phenytoin	1	0
Drugs with QT-prolongation potential[b], *n*		
Ondansetron/ondansetron hydrochloride	42	12
Levofloxacin	41	15
Median (range) treatment cycles	3 (1–35)	2 (1–9)
OS, months, median (80% CI)	8.8 (6.9–9.9)	4.9 (3.5–6.0)
Complete remission, %	17.0	2.3
Common all-causality AEs associated with SMO inhibitors, %		
Alopecia	<20	<20
Dysgeusia	25.0	2.4
Fatigue	31.0	19.5
Gastrointestinal disorders		
Nausea	35.7	12.2
Decreased appetite	33.3	12.2
Diarrhea	27.4	22.0
Constipation	25.0	14.6
Vomiting	21.4	9.8
Hematological toxicities		
Anemia	45.2	41.5
Febrile neutropenia	35.7	24.4
Thrombocytopenia	31.0	26.8
Musculoskeletal disorders		
Muscle spasms	22.6	4.9
Musculoskeletal pain[c]	≥20	≥20
Rash[c]	≥20	≥20
QTcF >500 ms	6.0	11.8
BRIGHT AML 1003 population – data from [50–52] and unpublished data	(*N* = 78)	(*N* = 38)
Survival probability at 1 year, %	39.4	8.4
Survival probability at 2 years, %	19.0	2.8
Complete remission, %	19.2	2.6
Median (range) time to complete remission, days	59 (33–919)	170[d]
Achieved transfusion independence, %	29.3	5.6
Median duration, days	212	144
Median time to ANC ≥1000/μL, days	27	13
Median (range) time to first recovery, days	27 (7–114)	13 (8–70)
Median time to ANC ≥500/μL, days	16	11
Median (range) time to first recovery, days	16 (3–143)	11 (8–119)
Median time to platelets ≥1,00,000/μL, days	30	26
Median (range) time to first recovery, days	30 (6–171)	26 (2–56)
Median time to platelets ≥50,000/μL, days	26	24
Median (range) time to first recovery, days	26 (4–141)	24 (2–119)

AE: adverse event; ANC: absolute neutrophil count; CI: confidence interval; CYP: cytochrome P450; IC: intensive chemotherapy; LDAC: low-dose cytarabine; OS: overall survival; QTcF: QT interval corrected for heart rate using Fridericia's formula; SMO: smoothened.

[a]One grade 3 AE of prolonged QT interval was considered related to fluconazole.

[b]Five patients (two receiving a concomitant QT-prolonging medication) had QTcF >480 ms and/or increase >60 ms from baseline, but no event was accompanied by serious arrhythmias.

[c]From glasdegib product label [35].

[d]Only one patient achieved complete remission; therefore, no range available.

Table 5. Summary of considerations for glasdegib use.

Consideration	Use of glasdegib
Baseline risk factors	
Age	Can be used in patients ≥75
Cytogenetic risk	Can be used in patients of all ELN risk groups
Ineligible for IC	Can be used in patients who have comorbidities that preclude use of intensive induction chemotherapy
Secondary AML	Can be used in patients with secondary AML
Mutations	Can be used in patients with AML who do not present with therapy-targeted mutations
Comorbidities	
General comorbidities	Can be used in patients who have comorbidities that preclude use of intensive induction chemotherapy
Cardiac disease	Can be used in patients with severe cardiac disease
Renal impairment	No glasdegib dose adjustment required for mild, moderate, or severe renal impairment
Hepatic impairment	No glasdegib dose adjustment required for mild, moderate, or severe hepatic impairment
Cytopenias	Can be considered for patients with the possibility of prolonged cytopenias, who may be frail, who experienced toxicities with venetoclax, or who are ineligible for venetoclax treatment
Gastrointestinal comorbidities	Evaluate for the potential to increase the risk of gastrointestinal AEs, and ensure that any prophylactic or supportive care therapies are initiated
Musculoskeletal comorbidities	Evaluate for the potential to increase the risk of musculoskeletal AEs, and ensure that any prophylactic or supportive care therapies are initiated
Concomitant medications	
Strong CYP3A inhibitors, e.g. azole antifungals, macrolide antibiotics, protease inhibitors	If coadministration is necessary, monitor patients for increased risk of AEs
Strong CYP3A inducers, e.g. bosentan, carbamazepine, dexamethasone, phenytoin, rifampin	Avoid coadministration
QTc-prolonging agents, e.g. antiarrythmics, antimalarials, macrolide antibiotics	Consider alternative therapies, if possible If coadministration is necessary, monitor patients for increased risk of QTc prolongation
Proton pump inhibitors, e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole	No restrictions on the use of proton pump inhibitors with glasdegib

AE: adverse event; AML: acute myeloid leukemia; CYP: cytochrome P450; ELN: European LeukemiaNet; IC: intensive chemotherapy; QTc: QT interval corrected for heart rate.

AML pathogenesis and the persistence of leukemic stem cell (LSC) populations [63–66]. Based on the known mechanism of action of SMOi, glasdegib may eradicate early LSC progenitor populations by reducing LSC dormancy and promoting the differentiation and cell cycle progression of LSCs [67,68].

Glasdegib plus LDAC use is dependent on clinical and patient factors, comorbidities, and concomitant medications (Table 5). Results from BRIGHT MDS&AML 1003 that have helped inform the use of glasdegib plus LDAC are presented in Table 4.

Baseline risk factors and disease characteristics

Age is important but should not be the only selection criterion, except perhaps in the upper range [13,15,17]. However, increased age is generally associated with poorer outcomes. Older patients may have poorer ECOG PS and general health and present with specific comorbidities that can impact treatment tolerability [2,8,13,15–17]. Concerns surrounding use of IC in older patients with AML stems from the risk of prolonged myelosuppression and high mortality [13,19–29]. In this context, glasdegib plus LDAC can be considered a first-line treatment for patients aged ≥75 [35].

Although glasdegib plus LDAC is approved for patients ineligible for IC, no standard guidelines exist to determine IC eligibility. The BRIGHT MDS&AML 1003 study pre-specified the criteria used to consider a patient to be ineligible for IC, making it more objective than most other studies. Available evaluation tools include the hematopoietic cell transplantation-specific or Charlson comorbidity indexes [9,13,15,17], and models incorporating multiple characteristics [9,13,17,69–72]. Irrespective of the guidelines used, lower-intensity treatments such as glasdegib plus LDAC or venetoclax plus HMAs can be considered for patients with AML ineligible for IC due to existing comorbidities.

Patients with sAML tend to have a poor prognosis, with reduced CR rates and OS [73–76]. BRIGHT MDS&AML 1003 demonstrated glasdegib plus LDAC efficacy in older patients with sAML; CPX-351 is another option, but should be administered only to patients who are eligible for IC and able to withstand prolonged myelosuppression.

Although glasdegib plus LDAC may be effective in patients with therapy-targetable mutations, treatments based on FLT3 or IDH inhibitors should be given priority consideration when mutations of those genes are identified.

Comorbidities

In a renal impairment study, participants with moderate or severe impairment had similar pharmacokinetic (PK) parameters following a single glasdegib 100-mg dose [77]. Coupled with the known safety profile of glasdegib [40,50], this suggests lower starting doses (<100 mg) may not be required in renal impairment. Glasdegib is largely eliminated through hepatic metabolism [78]. In a population PK analysis, glasdegib PK was unaffected by mild hepatic impairment [79]. In a hepatic impairment study, moderate or severe (Child-Pugh class B or C) impairment did not have a clinically meaningful effect on glasdegib exposure following a single 100-mg dose, although long-term data are warranted [80]. Together with previous studies, these data suggest dose modifications are not required in hepatic impairment [80].

In patients ineligible for IC, cytopenias occurred more frequently with glasdegib plus LDAC versus LDAC but were not accompanied by increased rate of sepsis or bleeding [51]. It is thought that higher absolute rates of cytopenia were due to longer treatment duration with glasdegib plus LDAC compared with LDAC [40]. With cytopenia rates adjusted to exposure, transfusion requirements were lower in patients treated with glasdegib plus LDAC. Glasdegib plus azacitidine did not substantially increase hematologic toxicities, cytopenic complications, or AEs related to cytopenias versus azacitidine [54]. As a result of the prolonged myelosuppression reported with HMAs plus venetoclax, glasdegib plus LDAC can be a treatment option when the treating physician considers the patient to be at higher risk of prolonged cytopenias, or when there might be limited access to transfusions or emergency care for neutropenia-related infections. Additionally, glasdegib plus LDAC is an alternative for patients ineligible for venetoclax due to risk of severe, long-lasting myelosuppression or previous toxicities with venetoclax.

Prior to initiating treatment in older patients or those unfit for IC, evaluate medical history and comorbidities regarding AEs commonly associated with SMOi, including alopecia, muscle spasms, musculoskeletal pain, and gastrointestinal AEs [35,81–84]. Patients should be educated on AE signs, symptoms, and appropriate management strategies. Prophylactic or supportive-care therapies should be initiated with glasdegib plus LDAC treatment. As an oral medication, glasdegib does not require in-clinic administration and may be preferred for frail patients, particularly when transfusions or IV administration will affect quality of life (QoL).

Concomitant medications

A full review of concomitant medications is essential to identify potential drug–drug interactions with glasdegib and modify treatment plans appropriately before initiating therapy.

Patients undergoing treatment for AML are at increased risk of fungal infections; antifungal agents are routinely used to manage this or as prophylaxis [85]. Azoles, the most commonly administered antifungals [85], inhibit cytochrome P450 (CYP) 3A4, and glasdegib is largely metabolized by the CYP system. In a healthy participant study, coadministration of glasdegib with ketoconazole elicited 140% and 40% increases in glasdegib plasma exposure and peak concentration, respectively [78,86]. In BRIGHT MDS&AML 1003, comparisons between patients who received CYP3A4 inhibitors versus those who did not were limited due to differences in exposure; however, rates of AEs and grade 3–4 AEs were 93.3% versus 100%, and 90% versus 82.5%, respectively (unpublished data). The glasdegib product label advises use of alternatives to strong CYP3A inhibitors [35]. However, if coadministration is required, modify doses and monitor patients for AEs. The benefit of antifungals outweighs the risks; monitor the corrected QT interval (QTc) after 1, 2, and 4 weeks when azoles are coadministered with glasdegib.

Glasdegib exposure and plasma concentrations in healthy participants are ≈70% and 35% lower, respectively, when coadministered with the CYP3A4 inducer rifampin [87]. Avoid concomitant use of glasdegib with strong CYP3A4 inducers (e.g. rifampin, bosentan, dexamethasone, carbamazepine, and phenytoin) [35]; dexamethasone should not be used as an antiemetic in patients receiving glasdegib. If coadministration with moderate CYP3A4 inducers is required, modify doses and monitor patients for AEs [35].

Avoid coadministration of glasdegib with QT-prolonging agents (e.g. antiarrythmics, antimalarials, and macrolides). If coadministration is necessary, monitor patients for QT prolongation [35]; monitor potassium and magnesium closely and correct abnormalities.

Two studies in healthy participants demonstrated that glasdegib can be administered with proton pump inhibitors, irrespective of food intake [88,89], which simplifies dosing recommendations and may facilitate adherence. Allopurinol, furosemide, and paracetamol may also be coadministered with glasdegib [40].

Response monitoring

Patients should not be removed from glasdegib plus LDAC treatment due to lack of CR alone. Improvement

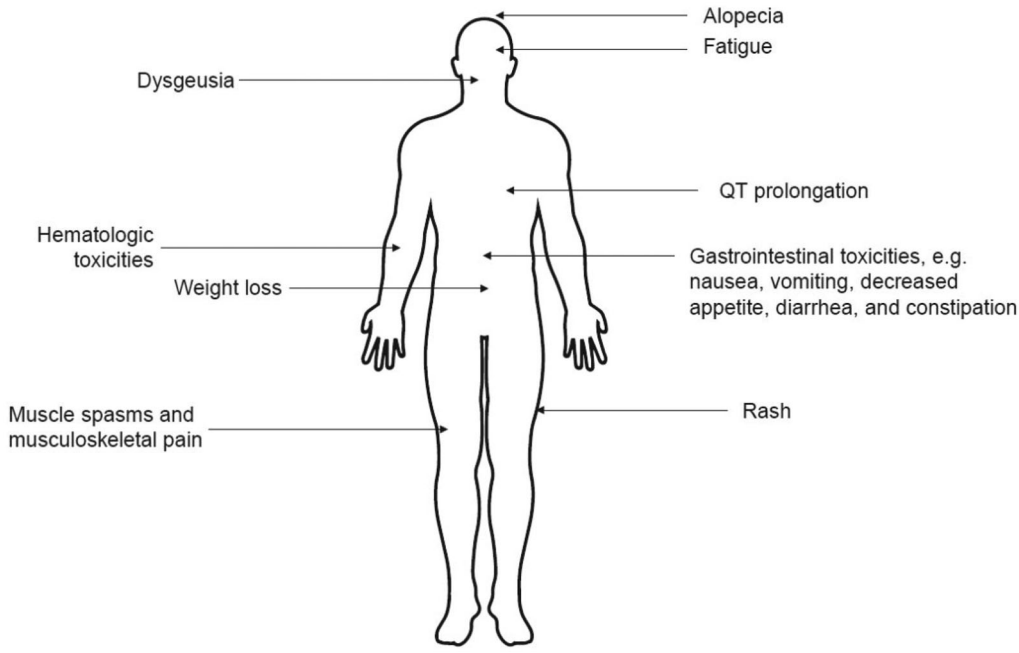

Figure 2. The most common adverse events associated with glasdegib.

(e.g. in transfusion requirements) in the absence of CR is compatible with, but not confirmatory for, glasdegib's action on LSCs rather than as a cytotoxic agent [35]. The panel recommended, in the absence of AML progression, patients receive ≥6 treatment cycles per product label, even if CR is not observed by cycle 2–3, particularly if other clinical benefits are seen.

Managing AEs associated with glasdegib plus LDAC

The most common AEs with glasdegib (Table 5 and Figure 2) are related to the mechanism of action of SMOi [90–95], although frequency and severity varies due to different PK properties. Most can be managed with dose modifications and/or temporary interruptions; however, alternative strategies are available (Table 6) [35,81–84]. In general, complete blood counts, electrolytes, and renal and hepatic function should be assessed prior to initiating treatment and at least weekly for the first month. Electrolytes and renal function should be monitored monthly throughout treatment [35].

Common non-hematologic AEs observed during glasdegib treatment include alopecia, dysgeusia, fatigue, gastrointestinal AEs, muscle spasms, and rash (Table 5) [40]. It is important to inform patients of the possibility of these AEs and that they are common with SMOi treatment. Additionally, a full review of the patient's medical history, comorbidities, underlying deficiencies, and concomitant medications should be completed before initiating treatment to identify contributory factors for AEs. Pharmacologic/supportive care therapies or nonpharmacologic management strategies should be considered, and existing treatments may need to be modified, either prophylactically or in the event of an AE [81–84]. Patients should be advised to maintain healthy physical activity, and nutritional and sleeping habits. Guidance should be provided on any behavioral changes that can minimize the risk of certain AEs [81–84]. If necessary, AEs can be managed by reducing or interrupting the glasdegib and/or LDAC dose [35].

For non-hematologic grade 3 AEs, glasdegib and/or LDAC should be interrupted until symptoms become mild or return to baseline [35]. Glasdegib can then be resumed at the same dose level or reduced to 50 mg. If toxicity recurs once, the dose should be reduced (if not done previously), and treatment should be discontinued upon second recurrence. If the AE is glasdegib related, LDAC may be continued, or vice versa [35]. Treatment should be discontinued in the event of non-hematologic grade 4 AEs [35].

Although glasdegib is associated with anemia and thrombocytopenia [40], these conditions are often present at baseline and causality is difficult to assess in the setting of active leukemia. Patients should be monitored regularly for myelosuppression and be advised of the potential for hematologic AEs. Ensuring that patients report symptoms (e.g. bruising easily,

Table 6. Summary of the management of the most common AEs associated with glasdegib [35,81–84].

Adverse event	AE severity	Examples of suggested AE management strategies
Alopecia	Grade 0 and general prophylaxis	Advise patients on the possibility of alopecia, and reassure them that hair typically begins to regrow upon cessation of treatment
		Educate patients with respect to sun protection and the avoidance of certain chemicals/irritants in order to support hair and scalp health
		Assess patients for comorbidities or underlying nutrient deficiencies that may contribute to alopecia
		May consider prophylactic treatment with minoxidil or oral dihydrotestosterone inhibitors
	Grade 1–2	May consider treatment with minoxidil or oral dihydrotestosterone inhibitors
		For eyelashes, may consider treatment with bimatoprost
		Suggest the use of a wig/hairpiece or to shave remaining hair
Dysgeusia	Grade 0 and general prophylaxis	Nutritional and dietary assessment prior to initiating treatment
		Educate patients on dietary strategies such as smaller and more frequent meals, use of stronger seasoning and flavor enhancers, and to increase chewing time
		Address any potential issues regarding oral hygiene, postnasal drip, or oral infections
	Grade 1–2	Periodic monitoring of zinc levels and supplementation of zinc
		Provide nutritional support
		If fluid intake is poor, assess renal function
	Grade $\geq$3	Employ management strategies listed for grade 1–2 AEs
		Consider glasdegib interruptions or dose modifications as advised in the product label for non-hematologic AEs
Fatigue	Grade 0 and general prophylaxis	Assess patients for other symptoms, sleep disturbances, nutritional deficiencies, comorbidities, or concomitant medications that may contribute to fatigue
		Advise patients to maintain regular physical activity
	Grade 1–2	Provide access to well-being and mindfulness programs
		Consider rehabilitation and psychology consultations
		Cognitive behavioral therapies or treatment with psychostimulants
		Assess for anemia, and treat if positive
	Grade $\geq$3	Employ management strategies listed for grade 1–2 AEs
		Consider glasdegib interruptions or dose modifications as advised in the product label for non-hematologic AEs
Gastrointestinal toxicities, e.g. nausea, vomiting, decreased appetite, diarrhea, and constipation	Grade 0 and general prophylaxis	Patient education on potential symptoms
		Take medication at nighttime or with food
		Eat small meals
		Remain hydrated and minimize caffeine intake
		Include ginger in the diet
		Avoid fatty, fried, or sweet foods
		Avoid pungent odors
	Grade 1–2	Treatment with antiemetics, e.g. antidopaminergic (metoclopramide or domperidone), serotonin receptor antagonist (ondansetron), antihistamine (dimenhydrinate), phenothiazine, or steroid medications
		Treatment with antidiarrheal medications, e.g. loperamide and trimebutine
		Treatment with stool softeners for constipation
		Oral fluid replenishment in cases of vomiting and/or diarrhea
	Grade $\geq$3	Employ management strategies listed for grade 1–2 AEs
		Consider glasdegib interruptions or dose modifications as advised in the product label for non-hematologic AEs
Hematologic toxicities	Grade 0 and general prophylaxis	Assess complete blood counts prior to treatment initiation and at least weekly for the first month of treatment
		Assess patients for comorbidities or concomitant medications that may contribute to hematologic toxicities
		Patient education on symptom monitoring, e.g. bruising easily, unexpected bleeding, blood in urine or stools
	Platelets $<10 \times 10^9$/L for >42 days in the absence of disease	Permanently discontinue glasdegib treatment
	Neutrophil count $<0.5 \times 10^9$/L for >42 days in the absence of disease	Permanently discontinue glasdegib treatment
Muscle spasms and musculoskeletal pain	Grade 0 and general prophylaxis	Obtain serum creatine kinase levels prior to initiating treatment and, where necessary, during treatment, e.g. if muscle symptoms are reported
		Advise the patient to maintain adequate hydration and provide education on passive stretching/gentle physical activity
	Grade 1–2	Examples of non-pharmacologic management include: massage; heat therapy, e.g. thermal compresses; tonic water or sports drinks as part of fluid intake; transcutaneous electrical nerve stimulation
		Examples of pharmacologic management include: electrolyte replacement; calcium channel blockers, e.g. amlodipine; muscle relaxants, e.g. cyclobenzaprine
		In the case of abdominal symptoms: calcium channel blockers or antimuscarinic agents
	Grade $\geq$3	

(*continued*)

Table 6. Continued.

Adverse event	AE severity	Examples of suggested AE management strategies
		Employ management strategies listed for grade 1–2 AEs
		Consider glasdegib interruptions or dose modifications as advised in the product label for non-hematologic AEs
QTc prolongation	Grade 0 and general prophylaxis	Assess electrolyte levels and supplement as clinically indicated
		Assess patients for comorbidities or concomitant medications that may contribute to QTc prolongation
		Monitor ECGs prior to initiation of treatment, for 1 week after treatment initiation, then once monthly for the next 2 months
	QTc interval 480–500 ms	Review and adjust concomitant medications
		Assess and correct electrolyte abnormalities
		Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation to $\leq$480 ms
	QTc interval $>$500 ms	Review and adjust concomitant medications
		Assess and correct electrolyte abnormalities
		Interrupt glasdegib treatment, and resume glasdegib treatment at a reduced dose of 50 mg QD when QTc interval returns to within 30 ms of baseline or $\leq$480 ms
		Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation
		Consider re-escalating to glasdegib 100 mg/day if an alternative etiology for the QTc prolongation is identified
	QTc interval prolongation with life-threatening arrhythmia	Permanently discontinue glasdegib treatment
Rash	Grade 0 and general prophylaxis	Patient education on behavioral changes, e.g. avoiding prolonged exposure to hot water and baths, using sunscreen regularly, and avoiding tight clothes
	Grade 1–2	Consider supportive care therapies, such as hypoallergenic moisturizing creams and topical therapy in the form of steroids, antiseptics, antibiotics, and/or antihistamines
		Consider support from a dermatologist
	Grade $\geq$3	Employ management strategies listed for grade 1–2 AEs
		Consider glasdegib interruptions or dose modifications as advised in the product label for non-hematologic AEs
Weight loss	Grade 0 and general prophylaxis	Nutritional and dietary assessment prior to starting treatment
		Assess patients for risk factors, comorbidities or underlying nutrient deficiencies that may contribute to weight loss
	Grade 1–2	Provide nutritional or dietary support
		Treatment with supplements, corticosteroids (excluding dexamethasone), or appetite stimulants, e.g. megestrol acetate or dronabinol
	Grade $\geq$3	Employ management strategies listed for grade 1–2 AEs
		Consider glasdegib interruptions or dose modifications as advised in the product label for non-hematologic AEs

AE: adverse event; ECG: electrocardiogram; QD: once daily; QTc: QT interval corrected for heart rate.

unexpected bleeding, blood in urine or stools, fever, extreme fatigue) can help identify AEs early in the treatment process. As detailed in the product label, glasdegib plus LDAC should be permanently discontinued with platelets $<10 \times 10^9$/L and neutrophil count $<0.5 \times 10^9$/L for $>$42 days in the absence of persistent disease [35]. Transfusions, granulocyte colony-stimulating factor, and antibacterial prophylaxis should be used per local guidelines.

The possibility of febrile neutropenia and associated complications increases with age, poor WHO performance score, and comorbidities [96]. Prophylactic antimicrobial treatment should be considered in at-risk patients and patients should be advised to report symptoms promptly (e.g. increased body temperature, chills, and sweating) [96]. For management, granulocyte colony-stimulating agents should be considered, particularly with difficult-to-control infections. In the event of neutropenic fever, patients should report immediately to the clinic or emergency center. Prompt assessment, identification, and treatment with antimicrobial therapy is important (e.g. IV broad spectrum antibiotics $\leq$1 h of occurrence), as well as ongoing monitoring of response, with therapy plan modifications as appropriate [96].

QTc prolongation is uncommon but needs awareness. In addition to monitoring electrolyte levels (particularly magnesium and potassium) and electrocardiograms (ECGs) throughout treatment, evaluating patients for comorbidities and QT-prolonging concomitant medications is important. Further details on managing specific QTc interval events are shown in Table 6 [35]. A pooled analysis of glasdegib trials ($N=$ 412) revealed no events of torsades de pointes (unpublished data).

Other AEs listed on the product label are dyspnea, edema, and hemorrhage (each $\geq$20% in product label). It is important to discuss the possibility of AEs with patients prior to treatment initiation, evaluate comorbidities and concomitant medications that may

lead to increased risk of AEs, and ensure patients are given the necessary information on AE signs and symptoms. Weight loss (<20% in BRIGHT MDS&AML 1003) is multifactorial and may result from other AEs or leukemia itself. As some patients may view weight loss as desirable rather than an AE, emphasize the importance of reporting any changes in body weight [35,81–84].

Summary

Glasdegib is the first SMOi approved for treatment of AML and targets the LSC population that can persist following standard chemotherapy. Treatment selection is multifactorial and includes patient age, comorbidities, concomitant medications, and risk factors. In contrast with other therapies, glasdegib 100 mg QD plus LDAC 20 mg BID can be considered for older patients (≥75) and patients with poorer risk profiles and prognostic scores, ineligible for IC, with sAML, or who received prior HMAs for MDS. As an oral medication, glasdegib does not require in-clinic administration. Additionally, glasdegib plus LDAC can be administered to patients with renal or hepatic impairment and severe cardiac disease. Prior to treatment initiation, a full evaluation of medical history, concomitant medications, and comorbidities should be performed. Patients should be educated on common AEs and mitigation strategies and regularly monitored for AEs during treatment. Key management strategies for common treatment-related AEs are dose modifications and interruptions. Effective AE management can lead to improved patient outcomes, QoL, and medication adherence.

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