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Glasdegib: A Novel Hedgehog Pathway Inhibitor for Acute Myeloid Leukemia

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Abstract

Acute myeloid leukemia (AML) is an aggressive myeloid disorder that is associated with a generally poor prognosis. Effective treatment options have been limited for older patients with AML who are not able to undergo intensive remission induction chemotherapy due to advanced age or comorbidities. New and novel agents are needed to improve treatment outcomes for this patient population. Glasdegib is a novel Hedgehog signaling pathway inhibitor approved by the U.S. Food & Drug Administration for the treatment of patients with newly diagnosed AML who are 75 years of age or older or who have comorbidities that preclude intensive induction chemotherapy. Glasdegib is approved in combination with low-dose cytarabine (LDAC). This approval is based on the results of a multicenter, open-label, randomized trial of glasdegib plus LDAC vs. LDAC monotherapy in which the addition of glasdegib resulted in an improvement in median overall survival.

Acute myeloid leukemia (AML) is an aggressive myeloid stem cell disorder that causes bone marrow failure. It is the most common acute leukemia in adults, with an estimated 21,450 new diagnoses and 10,920 deaths in 2019 (Siegel, Miller, & Jemal, 2019). The median age of diagnosis is 67 years (Klepin, Rao, & Pardee, 2014). The standard of care for AML has been induction therapy with 7+3, the combination of continuous infusion cytarabine and bolus dosing of an anthracycline delivered over 7 and 3 days, respectively. However, the use of intensive induction chemotherapy can be limited in some patients with AML due to advanced age or comorbidities.

Older patients with AML have historically been treated with less aggressive regimens such as low-dose cytarabine (LDAC) and hypomethylating agents (azacitidine and decitabine). Unfortunately, response rates and survival are typically low with less aggressive therapies. Studies evaluating LDAC have revealed response rates as low as 8%, with median overall survival (OS) of approximately 5 months (Kantarjian et al., 2012). When administered as monotherapy, hypomethylating agents demonstrate modest improvements, with response rates of about 18% and

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median OS of 7.7 months (Kantarjian et al., 2012). Also, older patients with AML may have had antecedent myelodysplastic syndrome (MDS), in which they may have already received treatment with a hypomethylating agent, necessitating the need for alternative therapy. There has been a need for new and novel therapeutic strategies for this difficult-to-treat patient population.

In November 2018, the U.S. Food & Drug Administration (FDA) granted approval of glasdegib (Daurismo) for the treatment of newly diagnosed AML in patients who are 75 years of age or older or who have comorbidities that preclude intensive induction chemotherapy based on the results of a multicenter, open-label, randomized trial (Cortes et al., 2019). Glasdegib is to be administered in combination with LDAC.

PHARMACOLOGY AND PHARMACOKINETICS

The Hedgehog signaling pathway plays a key role in embryogenesis. It is usually silenced in adults, as it is repressed shortly after birth (Ok, Singh, & Vega, 2012). Aberrant signaling of this pathway has been implicated in leukemic stem cell survival and expansion. Chemotherapy-resistant myeloid leukemia cells have been shown to overexpress components of the Hedgehog pathway, and inhibition of this can enhance sensitivity to chemotherapy (Irvine & Copland, 2012). The activation of the Hedgehog pathway is dependent on Smoothened, a transmembrane protein. Glasdegib inhibits the activation of the Hedgehog signaling pathway by binding to Smoothened (Fukushima et al., 2016). When administered in combination with chemotherapy, glasdegib sensitizes cells via Hedgehog pathway inhibition, thereby reducing chemotherapy resistance and the progression of leukemic cells.

A phase I dose-escalation and pharmacokinetic (PK) study evaluated glasdegib in 47 patients with myeloid malignancies (Martinelli et al., 2015). This study revealed dose-proportional increases in plasma concentrations, with doses ranging from 5 to 600 mg daily. Steady state was reached after 8 days of administration. The median elimination half-life at the maximum tolerated dose of 400 mg daily was 23.9 hours. The bioavailability of glasdegib was found to be 77.12% in healthy volunteers after administration of 100 mg in a fasted state (Pfizer Laboratories, 2018).

In a phase II study of glasdegib at 100 mg orally once daily plus LDAC, PK analysis of glasdegib was performed in 41 dose-compliant patients not concurrently on CYP450 inhibitors (Cortes et al., 2019). Pharmacokinetic parameters were calculated: maximum concentration (C_{max}) of 1,252 ng/mL, median time to C_{max} of 1.7 hours, steady-state concentration of 718 ng/mL, and predose plasma concentration of 427 ng/ml. Glasdegib was administered to patients in a fasted state in this trial.

CLINICAL EFFICACY

The efficacy and safety of glasdegib/LDAC was compared to LDAC alone in a randomized, open-label, multicenter phase II trial of older patients with newly diagnosed AML or high-risk MDS (Cortes et al., 2019). Subjects were randomized to receive cytarabine at 20 mg subcutaneously twice daily on days 1 through 10 of a 28-day cycle either alone or in combination with glasdegib at 100 mg po daily. The primary endpoint was OS. Secondary endpoints included response rates.

A total of 88 patients received glasdegib/LDAC and 44 received LDAC monotherapy. Approximately 87% of the patients had AML; the remaining 13% had high-risk MDS. The primary endpoint of median OS was 8.3 months with glasdegib/LDAC compared to 4.9 months with LDAC alone (hazard ratio, 0.51; 80% confidence interval = 0.386–0.675; p = .0002). In patients with AML, the overall response rate (ORR) with glasdegib/LDAC and LDAC alone were 26.9% and 5.4%, respectively. The ORR in patients with MDS was 20% with glasdegib/LDAC and 0% with LDAC alone. The authors concluded that glasdegib/LDAC resulted in an improvement in OS and ORR compared to LDAC alone and may be a potential treatment option for patients with newly diagnosed AML who are unfit for intensive chemotherapy.

ADVERSE DRUG REACTIONS

Common adverse events (≥ 25%) of any grade associated with glasdegib/LDAC include anemia, thrombocytopenia, febrile neutropenia, nausea, decreased appetite, pneumonia, diarrhea, pyrex-

Table 1. Common Adverse Events of Glasdegib/LDAC (Occurring ≥ 25%)

	All grades (%)	Grades 3–4 (%)
Hematologic toxicity		
Anemia	45.2	41.7
Thrombocytopenia	31	31
Gastrointestinal toxicity		
Nausea	35.7	2.4
Decreased appetite	33.3	3.6
Diarrhea	27.4	4.8
Constipation	25	1.2
Dysgeusia	25	0
Serious toxicity		
Febrile neutropenia	35.7	35.7
Pneumonia	28.6	16.7
Other toxicity		
Fatigue	31	14.3
Pyrexia	27.4	2.4
Peripheral edema	26.2	0

Note. LDAC = low-dose cytarabine. Information from Cortes et al. (2019).

ia, peripheral edema, constipation, and dysgeusia (Cortes et al., 2019; Table 1). Serious (grade 3 or 4) adverse events occurred more frequently in the glasdegib/LDAC (64.3%) arm compared with LDAC alone (56.1%). The most frequently reported serious adverse events with glasdegib/LDAC were febrile neutropenia (35.7%) and pneumonia (16.7%).

QTc interval prolongation has also been reported with glasdegib. Approximately 5% and 4% of patients in trials evaluating glasdegib experienced a QTc prolongation of > 500 msec and an increase of > 60 msec from baseline, respectively (Pfizer Laboratories, 2018).

ADMINISTRATION AND DOSING

The recommended initial dose of glasdegib is 100 mg daily in combination with cytarabine at 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle (Pfizer Laboratories, 2018). Six cycles of this regimen should be completed before assessment of clinical response. Administration of glasdegib should continue until disease progression or intolerability. If grade 3 or higher adverse events occur, glasdegib/LDAC should be interrupted until improvement to at least grade 1. Glasdegib can then be restarted at a decreased dose of 50 mg daily. Cytarabine can be continued at the 20-mg twice-daily dose or decreased to 10 to 15 mg twice daily. Recurrence of toxicity should lead to permanent discontinuation of glasdegib; however, cytarabine can be continued if appropriate. Glasdegib should be discontinued permanently if life-threatening toxicity occurs.

IMPLICATIONS FOR THE ADVANCED PRACTITIONER

Glasdegib combined with LDAC offers the advanced practitioner a new option in the management of newly diagnosed AML for patients unfit for intensive induction chemotherapy. Severe cardiac disease, Eastern Cooperative Oncology Group performance status ≥ 2, or baseline creatinine > 1.3 mg/dL are examples of indications that may preclude a patient from receiving intensive remission induction (Cortes et al., 2019). While this is a new option for this patient population, there are a variety of other new agents that can be considered for older patients with newly diagnosed AML such as venetoclax/hypomethylating agent combinations, isocitrate dehydrogenase (IDH) inhibitors (ivosidenib and enasidenib) for *IDH1/2*-mutant AML, and gemtuzumab ozogamicin for CD33-positive AML (Amadori et al., 2016; DiNardo et al., 2018a, 2018b; Stein et al., 2017). To date, glasdegib/LDAC has not been compared to any of these newer agents. Additionally, there is a lack of data investigating the safety and efficacy of glasdegib in patients with relapsed/refractory AML who have progressed on other novel agents. Currently, the preferred treatment in the National Comprehensive Cancer Network Guidelines for newly diagnosed patients with AML not eligible for intensive induction chemotherapy is venetoclax in combination with a hypomethylating agent or LDAC (National Comprehensive Cancer Network, 2019). In lieu of being compared in a clinical trial to venetoclax-based combinations, it is difficult to ascertain exactly where glasdegib/LDAC will fit into therapy for AML patients. It could be considered for patients with intolerability or contraindications to venetoclax-based regimens.

QTc Prolongation

As previously discussed, glasdegib can prolong the QTc interval; advanced practitioners can play a critical role in the monitoring and management of this adverse event. Electrocardiogram should be evaluated prior to initiating glasdegib, approximately 1 week after starting glasdegib, and then at least once a month for the next 2 months. Serum electrolytes, such as potassium and magnesium, should be assessed and supplemented as needed with an increase in the QTc interval > 480 msec. Glasdegib should be interrupted for a QTc interval > 500 msec and permanently discontinued in the event of QTc interval prolongation in the presence of a life-threatening arrhythmia.

Patients should have their medications reviewed and adjusted for concomitant drugs that may also prolong the QTc interval since many of the supportive care medications used in AML patients can have this effect, such as antiemetics, azole antifungals, and fluoroquinolones.

Interactions

Beyond QTc interval drug-drug interactions, glasdegib is metabolized primarily through CYP3A4 and is prone to PK drug interactions with CYP3A4 inducers and inhibitors. Moderate CYP3A4 inducers can decrease the serum concentrations of glasdegib, potentially lowering its efficacy. Strong CYP3A4 inducers should be avoided with glasdegib therapy. Strong and moderate CYP3A4 inhibitors can decrease the metabolism of glasdegib, leading to increased exposure of the drug. Posaconazole and voriconazole are strong CYP3A4 inhibitors that are often used as antifungal prophylaxis in AML patients.

A phase Ib trial evaluating glasdegib at doses of 100 mg and 200 mg once daily did not find a maximum tolerated dose, and therefore the recommended phase II dose was 100 mg to account for the fact that patients may be on CYP3A4 inhibitors with antifungal prophylaxis (Savona et al., 2018). Based on this, it should be safe to administer glasdegib with moderate and strong CYP3A4 inhibitors.

Cost

An additional consideration for glasdegib is cost. A single 100-mg tablet and a 28-day supply of glasdegib costs approximately $677 and $18,956, respectively (UpToDate, 2019). Given that glasdegib, like many other new oncolytics, is an expensive medication, the advanced practitioner can help with facilitating the authorization process and patient assistance programs as needed to help mitigate financial toxicity.

CONCLUSION

Glasdegib is a novel Hedgehog pathway inhibitor indicated for the treatment of newly diagnosed AML in combination with LDAC for patients who are 75 years or older or who have comorbidities that preclude intensive induction chemotherapy. Studies comparing the efficacy of glasdegib with other agents in the frontline setting of AML in the older patient are needed to establish its place in therapy.

Disclosure

The authors have no conflicts of interest to disclose.

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