Clinical Cancer Research

Glasdegib with Low-Dose Cytarabine: A New Upfront Option for the Vulnerable AML Patient

Amir T. Fathi

A multitude of regulatory approvals has recently changed the therapeutic landscape of acute myeloid leukemia. Among these was upfront therapy with the Hedgehog inhibitor glasdegib with low-dose cytarabine. Understanding the process of and rationale for approval of this promising combination is timely and valuable for the oncology community.

See related article by Norsworthy et al., p. 6021

In this issue of *Clinical Cancer Research*, Norsworthy and colleagues (1) describe the process and rationale for the recent approval by the FDA of the combination of glasdegib and low-dose cytarabine (LDAC) for newly diagnosed acute myeloid leukemia (AML) in older patients or those with substantial comorbidity, limiting intensive treatment.

As recently as 5 years ago, therapeutic advancement in AML had remained stagnant for decades, ever since the emergence of anthracycline- and cytarabine-containing induction therapy decades prior. This landscape, however, has changed in dramatic fashion in the last few years, with a series of regulatory approvals for novel therapies. Among these were approvals for the IDH1 inhibitor ivosidenib, the IDH2 inhibitor enasidenib, and the FLT3 inhibitor gilteritinib, for patients with relapsed/refractory *IDH1/2*- and *FLT3*-mutated AML, respectively. FDA approvals also included those of novel combinations for newly diagnosed patients with historically poor outcomes and unsuitability for intensive treatments because of advanced age or high comorbidity burden. Among these are the combinations of hypomethylating agents with the BCL2 inhibitor venetoclax and the subject of the current article, LDAC combined with the smoothened (SMO) inhibitor glasdegib.

Glasdegib is a potent small-molecule inhibitor of SMO, an integral enzyme of the Sonic Hedgehog (HH) signaling pathway and implicated in the persistence of leukemic stem cells and therapeutic resistance in myeloid malignancies (Fig. 1). The HH signaling pathway is initiated by a series of secreted HH ligands, which directly inhibit a transmembrane protein called Patched1 (PTCH1). This, then in turn alleviates the inhibition of a coupled receptor called SMO. SMO regulates the activity of the GLI proteins, a family of transcription factors among whose target genes are several implicated in the pathogenesis of human malignancy (2). Under basal conditions, PTCH1 and SMO interaction is limited. When SMO is inactive, GLI proteins undergo proteolytic processing and are repressed. HH ligands trigger movement of PTCH1 into proximity, allowing interaction. Active SMO in turn promotes the conversion of active forms of GLI transcription factors, activating target genes. HH signaling appears to play a major role in the maintenance of the leukemic stem cells in myeloid malignancy. Studies have reported that SMO activity impacts hematopoietic stem cell function, that elevated levels of GLI promote chemotherapeutic drug resistance, and that the leukemic bone marrow environment is characterized by increased HH expression and release (2, 3). Therefore, the inhibition of this key pathway seemed to be a promising avenue for therapeutic development.

A series of small molecules were developed as inhibitors of the HH pathway and studied in human malignancy. As Norsworthy and colleagues detail in their article, glasdegib was highly promising in preclinical studies. It demonstrated a very high potency in cell-based models and marked synergy in combination with cytarabine in suppressing proliferation of leukemic myeloblasts in animal models. This data seemed to suggest that glasdegib had promising antileukemic activity and could theoretically overcome therapeutic resistance to the conventional cytotoxic agent, cytarabine, ultimately forming the basis to study glasdegib as monotherapy and in combination with conventional therapies in AML.

The basis of the FDA approval for the combination of LDAC, given at 20 mg subcutaneously twice daily on days 1–10 of 28-day cycles, and glasdegib administered orally at a dose of 100 mg once daily, was the BRIGHT AML 1003 study (NCT01546038). This trial included a phase II portion, which randomized patients, in 2:1 fashion, to receive the combination versus LDAC alone. The primary efficacy endpoint was overall survival (OS), and investigators assumed a median survival for LDAC monotherapy of 5 months. Complete remission (CR) rate was a secondary endpoint. Eligible patients were those aged 55 years or older with newly diagnosed AML or high risk myelodysplastic syndrome (MDS), but also had to meet one of the following criteria: age $\geq$ 75 years, substantial cardiac disease, performance status of 2, or creatine above 1.3 mg/dL (4).

As Norsworthy and colleagues detail, the study met its endpoint. Analysis of the intent-to-treat population revealed a superiority in OS for the combination compared with LDAC monotherapy (HR, 0.51; 95% confidence interval, 0.34–0.77; $P = 0.0004$). Among patients with AML who were treated with the combination, median OS was 8.3 months versus 4.3 months for monotherapy (HR, 0.46; $P = 0.0002$). These outcomes were

Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Amir T. Fathi, Zero Emerson Place, Suite 118, Boston, MA 02114. Phone: 617-724-1124; Fax: 617-724-1126; E-mail: afathi@mgh.harvard.edu

Clin Cancer Res 2019;25:6015–7

doi: 10.1158/1078-0432.CCR-19-1986

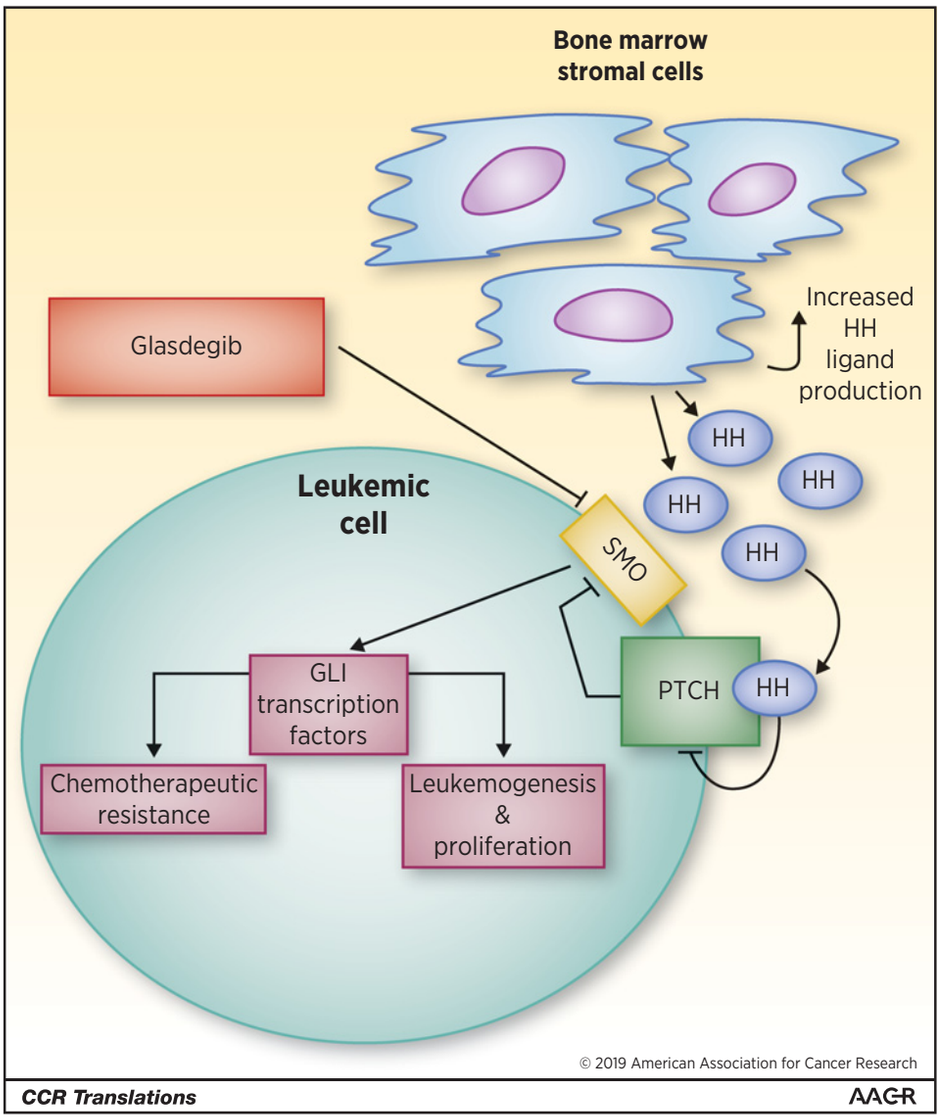

Figure 1.
Glasdegib is a potent, small-molecular inhibitor of the smoothened (SMO) protein, a key enzyme in the Hedgehog pathway, thought to promote persistence of leukemic stem cells and therapeutic drug resistance. In the normal setting of the marrow environment, the transmembrane protein PTCH1 are not in proximity. When SMO is inactive, GLI proteins undergo proteolytic processing and are repressed. However, high levels of HH ligand released by marrow stromal cells in the setting of myeloid malignancy trigger movement of PTCH1 into proximity of SMO, and release of repression. Active SMO thereafter promotes the conversion to active forms of GLI transcription factors, which through effects on target genes, leads to leukemic persistence, proliferation, and therapeutic resistance to chemotherapies.

ultimately persuasive enough, from an efficacy standpoint, to support approval. Of note, the number of MDS patients studied was deemed too low to make persuasive conclusions for this subpopulation. Rate of CR was also higher among those receiving the combination of glasdegib and LDAC (18.2% vs. 2.6%). The median time to CR among patients receiving the combination was 1.9 months, and the mediation duration of CR was 9.8 months.

In addition, an important consideration for the FDA was safety of the combination, and in general, this treatment approach was well-tolerated. Nonhematologic adverse events, including azotemia, electrolyte imbalance, hair loss, AST elevation, and CPK elevation, were more frequently seen among those receiving the combination. However, ≥grade 3 events were uncommon. QTc prolongation was also higher among those receiving the combination, including ≥grade 3 events, leading to cautionary guidance, but these were infrequent and occurred mainly in the initial month of therapy.

Taken together, the safety profile of the combination and the statistically significant improvement in OS for patient populations with traditionally grim prognoses was sufficiently persuasive to achieve regulatory approval. The combination of glasdegib and LDAC was demonstrated to be superior in efficacy when compared with LDAC alone, a conventional and longstanding treatment for older or less robust AML patients. However, some notes of caution linger. The CR rate for LDAC monotherapy (at 2.6%) on the BRIGHT AML 1003 study is markedly lower than that seen previously in other trials (5), and there is no clear reason for this. In addition, LDAC has not been the only conventional option for these vulnerable AML populations, and increasingly, they have been treated with the hypomethylating agents, azacitidine and decitabine. These agents have been associated with similar CR rates and are well-tolerated.

Furthermore, hypomethylating agents have similarly been studied in combination with novel agents, and one such combination, hypomethylating agent with venetoclax, was also recently approved by the FDA for an overlapping patient population. This combination, although impacted by a high incidence of therapy-induced cytopenias and drug interactions, has been associated

with much higher rates of response (67% CR + CRi and 37% CR; ref. 6) than seen historically with hypomethylating agent monotherapy, or with glasdegib and LDAC. The availability of hypomethylating agent and venetoclax combinations will likely limit the use of glasdegib and LDAC. Nevertheless, the latter remains yet another approved and well-tolerated option for those who may not be suitable for other therapies. Intriguingly, a subset of patients receiving LDAC and glasdegib on the randomized study had previously received hypomethylating agents, a population not traditionally associated with response following a rechallenge with hypomethylating agent–based treatment.

In summary, Norsworthy and colleagues describe the rationale and process of regulatory approval for the combination of glasdegib with LDAC for AML. In addition to reviewing the persuasive efficacy data that emerged from the BRIGHT AML 1003 study, the article also outlines the safety and tolerability considerations for the approval. We are indeed witnessing an exciting era of therapeutic advancement, particularly among those with traditionally poor risk AML such as older patients, those with comorbidity, and those with advanced disease.

Disclosure of Potential Conflicts of Interest

A.T. Fathi reports receiving other commercial research support from Celgene, Agios, Seattle Genetics, and Takeda, and is a consultant/advisory board member for Celgene, Agios, Pfizer, Takeda, Jazz, Astellas, Daiichi Sankyo, and Boston Biomedical. No other potential conflicts of interest were disclosed.

Received June 26, 2019; revised July 8, 2019; accepted July 16, 2019; published first July 19, 2019.

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