FDA Approves Glasdegib for Newly Diagnosed Acute Myeloid Leukemia

Background

- Glasdegib inhibits the hedgehog pathway by targeting Smoothened (SMO), which is a transmembrane protein involved in hedgehog signal transduction
    - The hedgehog pathway is involved in cell differentiation and self-renewal during embryogenesis and is later suppressed in adult tissues
- Leukemia stem cells have been shown to have an upregulation of the hedgehog signaling pathway, which contributes to the chemoresistance observed in acute myeloid leukemia (AML) cell lines
- Inhibition of SMO has been shown to reduce leukemic stem cell populations in AML patients, downregulate hedgehog target genes, and significantly reduce tumor burden

FDA Approval

- Glasdegib 100 mg orally once daily on days 1-28 without regard to meals in combination with low-dose cytarabine (20 mg subcutaneously twice daily on days 1-10 of each 28-day cycle) for the treatment of newly-diagnosed AML in adult patients who are >75 years old or who have comorbidities that preclude use of intensive induction chemotherapy

Efficacy

Cortes et al. Leukemia (2019) 33:379–389. (NCT01546038)

- Study Design: open label, multicenter phase II study
- Patients: Aged ≥55 years with newly diagnosed, previously untreated AML or high-risk MDS
    - 88 and 44 patients were randomized to glasdegib/LDAC or LDAC, respectively
    - AML (Glasdegib + LDAC vs. LDAC alone): 88.6% vs. 86.4%
    - Poor cytogenetic risk (Glasdegib + LDAC vs. LDAC alone): 40.9% vs. 43.2%
- Results (Glasdegib + LDAC vs. LDAC alone):
    - Median OS (mOS): 8.8 months vs. 4.9 months, p=0.0004
    - CR: 17.0% vs. 2.3%, p<0.05
    - mOS in patients with good/intermediate cytogenetic risk: 12.2 mos vs. 4.8 mos, p=0.0008
    - Nonhematologic grade 3/4 AEs included pneumonia and fatigue in the glasdegib + LDAC group

Toxicity

Most common AEs (≥20%): anemia, fatigue, hemorrhage, febrile neutropenia, musculoskeletal pain, nausea, edema, thrombocytopenia, dyspnea, decreased appetite, dysgeusia, mucositis, constipation, and rash

Black Box Warning	Major Adverse Effects
Embryo-fetal toxicity • Can cause embryo-fetal death or severe birth defects when administered to pregnant women • Pregnancy testing should be conducted in females of reproductive age • Effective contraception should be used in males and females during treatment with glasdegib and for at least 30 days after the last dose	QTc prolongation • For QTc 480-500 ms, monitor EKGs weekly for 2 weeks following resolution of QTc prolongation ≤ 480 ms • Interrupt glasdegib for QTc > 500 ms and resume glasdegib at 50 mg once daily when QTc returns to within 30 ms of baseline or ≤ 480 ms • Discontinue glasdegib permanently for patients with QTc prolongation and signs/symptoms of life threatening arrhythmia Blood donation: • Do not donate blood during treatment with glasdegib and for at least 30 days after last dose of glasdegib

Drug Interactions

- Avoid coadministration with strong CYP3A4 inducers or inhibitors (no dose adjustment recommendations)
- Avoid coadministration with other QTc prolonging drugs

Bottom Line

Glasdegib is well tolerated and efficacious for elderly patients with newly diagnosed AML. It represents a promising option for elderly patients who cannot tolerate intensive chemotherapy.

References

1. Daurismo (glasdegib) [prescribing information]. New York, NY: Pfizer, Inc; November 2018.
2. Cortes J et al. Leukemia (2019) 33:379–389