AMLGlobalPortal

General AML

ASH 2018 | Uproleselan (GMI-1271) plus chemotherapy in older patients with acute myeloid leukemia

Cynthia Umukoro | Dec 13, 2018

E-selectin (E-sel) is a cell adhesion molecule expressed constitutively in the bone marrow endothelium and is involved in cell signaling and chemotaxis. Binding of acute myeloid leukemia (AML) blasts to E-sel, can lead to activation of leukemic cell survival pathways, thereby contributing to chemotherapy resistance. Uproleselan (GMI-1271) is a novel antagonist of E-sel, which acts by disrupting leukemia cell survival pathways thus enhancing chemotherapy response. In AML tumor models, addition of uproleselan to chemotherapy improved clinical outcomes including survival.

At the 60th American Society of Hematology Annual Meeting & Exposition, Daniel J. DeAngelo from the Dana-Farber Cancer Institute, Boston, US, presented the final, correlative and subgroup analyses from a phase I/II study, which is evaluating the safety and efficacy of uproleselan in combination with standard chemotherapy, in patients with relapsed or refractory (R/R) AML, and also in AML patients 60 years of age and older with newly diagnosed disease.

In this phase I/II study, a total of 66 patients (median age = 59 years; range, 26–84) with relapsed (n = 44) or refractory (n = 22) AML were treated with escalating doses of uproleselan (5–20 mg/kg) for eight days (uproleselan was given 24 hours prior, every 12 hours during and 48 hours post-chemotherapy) in combination with mitoxantrone, etoposide, cytarabine (MEC) chemotherapy. The recommended phase 2 dose (RP2D) was 10 mg/kg. Fifty-four patients were treated at the RP2D.

Key findings in R/R AML patients:

- The most common grade 3–4 adverse events (AEs) were sepsis (18%), gastrointestinal (11%) and cardiac (9%)
- Grade 3–4 mucositis was 2% at RP2D
- Complete response (CR)/CR with incomplete count recovery (CRi) in all patients: 39% (26/66)
    - CR/CRi in patients treated at RP2D: 41% (22/54)
- 60-day mortality rate in all patients: 9% (6/66)
    - 60-day mortality rate in patients treated at RP2D: 9% (5/54)
- Duration of prior remission < 6 months in all patients: 23% (5/23)
    - Duration of prior remission < 6 months in evaluable patients treated at RP2D: 23% (5/23)
- Of the 16 evaluable patients for measurable residual disease (MRD), 11 were MRD negative
- Median follow-up time: 8.9 months
- Median overall survival (OS): 8.8 months (95% CI, 5.7–11.4)
    - Median OS in patients (n = 22) with early relapse (< 6 months): 5.1 months (95% CI, 3.2–9.4)

    - Median OS in patients (n = 22) with primary refractory disease: 6.7 months (95% CI, 3.1– 13.8)
- Patients with high expression of E-sel ligand (≥ 10% E-sel ligand) at baseline had a significantly longer OS compared to patients with low expression of E-sel ligand (< 10% E-sel ligand): median OS; 12.7 *vs* 2 months respectively, *P* = 0.0056

The phase II portion of this study enrolled 25 patients (median age = 67 years; range, 60–79) with newly diagnosed *de novo* (n = 12) or secondary (n = 13) AML were enrolled in this study. Patients were treated with uproleselan plus cytarabine and idarubicin (7+3) induction chemotherapy.

Key findings in newly diagnosed AML patients:

- The most common grade 3–4 AEs were colitis (12%), febrile neutropenia (68%) and respiratory (28%)
- No grade 3–4 mucositis was seen
- CR/CRi in all patients: 72% (18/25)
    - CR/CRi in patients with *de novo* AML: 75% (9/12)
    - CR/CRi in patients with secondary AML: 69% (9/13)
- 60-day mortality rate: 12% (3/25)
- Of the nine evaluable patients for MRD, five (56%) were MRD negative
- Median follow-up time: 13.0 months
- Median OS and event-free survival (EFS) in all patients were 9.2 months (95% CI, 3–12.6) and 12.6 months (95% CI, 9.9–NA), respectively
    - Median OS and EFS in patients with secondary AML were 10.5 months (95% CI, 4.4–NA) and 7.7 months (95% CI, 1.1–9.5), respectively

Daniel J. DeAngelo noted that the findings of this study indicate that uproleselan can be safely administered with chemotherapy. Encouraging clinical outcomes were observed in this study with high remission rates and promising survival outcomes. In addition, high E-sel expression is associated with improved remission and survival with uproleselan treatment in R/R AML.

The speaker concluded by stating that confirmatory trials of uproleselan in R/R and newly diagnosed AML are currently underway.

References

1. DeAngelo D. J. *et al.* Uproleselan (GMI-1271), an E-Selectin antagonist, improves the efficacy and safety of chemotherapy in relapsed/refractory (R/R) and newly diagnosed older patients with acute myeloid leukemia: final, correlative and subgroup analyses. 2018 Dec 2; Oral Abstract #331: 60th ASH Annual Meeting and Exposition, San Diego, CA.

2018-uproleselan-gmi-1271-plus-chemotherapy-in-older-patients-with-acute-myeloid-leukemia>