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General AML, TP53, NPM1

ASH 2018 | Venetoclax-based therapies for patients with acute myeloid leukemia who are ineligible for intensive chemotherapy

Cynthia Umukoro | Dec 12, 2018

Recently, a lot of attention has been focused on a promising agent in acute myeloid leukemia (AML), venetoclax. Venetoclax is an oral selective inhibitor of BCL-2 inhibitor, an anti-apoptotic protein that has been reported to play a key role in regulating apoptosis via the intrinsic mitochondrial cell death pathway. In AML, overexpression of the BCL-2 protein has been shown to be associated with poor outcomes and conferring chemotherapeutic resistance.

At the 60th American Society of Hematology (ASH) Annual Meeting & Exposition, there were several talks focused on the use of venetoclax in combination with hypomethylating agents (HMAs) or chemotherapy in patients with AML. On Sunday 2nd December 2018, there were two talks focused on the use of venetoclax in patients with AML who are ineligible for intensive chemotherapy.

One of these talks was given by Stephen A. Strickland from Vanderbilt University Medical Center, Nashville, TN. The speaker presented updated data from a phase I/II study (NCT02287233) on the efficacy and safety of venetoclax combined with low-dose cytarabine (LDAC) in patients with previously untreated AML, who are ineligible for intensive chemotherapy. Since treatment options for older patients with AML who are unfit for intensive chemotherapy are limited, this study is of importance in improving outcomes in older AML patients.

Data from this study have shown that the venetoclax-LDAC combination is tolerable and durable in elderly AML patients. Additionally, the recommended phase 2 dose (RP2D) of venetoclax in combination with LDAC was found to be 600 mg. Follow-up data presented at the 2017 ASH Annual Meeting showed that 600 mg venetoclax has a low early mortality rate and demonstrated a clinically durable activity in elderly patients with newly diagnosed AML who are eligible for intensive chemotherapy.[1]

The speaker presented data for patients treated at the RP2D. Eighty-two patients (median age = 74 years; range: 63–90) received venetoclax at 50 or 100 mg daily and dose escalated over 4–5 days to reach the RP2D. In subsequent 28 day cycles, venetoclax was administered at 600 mg on all days. LDAC (20 mg/m^2 daily) was subcutaneously administered on days 1–10 of each cycle.[2]

Key findings at data cut-off as of November 8, 2017:

Safety

- The most common grade 3–4 adverse events (AEs) across all patients were febrile neutropenia (42%), thrombocytopenia (38%), neutropenia (27%), and anemia (27%)

- Serious AEs observed in ≥ 5% of patients were anemia (31%), febrile neutropenia (27%), pneumonia (10%) and sepsis (7%)
- Grade 3 tumor lysis syndrome was observed in two patients

Efficacy

- Complete remission (CR)/ CR with incomplete blood count recovery (CRi) rate: 54%
  - Median time to first response: 1.4 months (range: 0.8–14.9)
  - Median time to best response: 2.8 months (range: 0.8–22.4)
  - Median duration of remission after CR/CRi: 8.1 months (95% CI, 5.3–14.9)
- Patients with selected genetic mutations achieved the following rates of CR/CRi: *TP53*, 30%; *IDH1/2*, 72%; *FLT3*, 44%; *NPM1*, 89%
- Median overall survival (OS): 10.1 months (95% CI, 5.7–14.2)
- Median OS in patients who achieved CR, CR/CRi and other responses: not reached (95% CI, 16.9–NR) vs. 18.4 months (95% CI, 14.0–NR) vs. 3.5 months (95% CI, 2.3–5.1)
- Early 30-day mortality rate: 6%
- Among patients that were RBC or platelet transfusion dependent at baseline, 48% (39/82) and 60% (49/82), respectively, achieved transfusion independence while on venetoclax therapy
- Minimal residual disease (MRD) assessment demonstrated that 32% (14/44) of patients with CR/CRi achieved MRD negative status (MRD negativity was defined as less than 10^{-3} leukemic cells at any measurement in bone marrow aspirates)

In summary, "venetoclax in combination with LDAC led to rapid, deep, and durable responses in patients with AML who were ineligible for intensive chemotherapy." Compared to historical rates with LDAC alone, venetoclax plus LDAC demonstrated an improved CR and survival in this group of patients.

Stephen A. Strickland concluded by stating that the findings of this study demonstrate that venetoclax in combination represents an effective therapeutic option for patients with AML who are not suitable for standard induction therapy.

The second talk was given by Daniel Pollyea, from the University of Colorado, Denver, US. The speaker presented updated results from a phase I dual-stage, non-randomized phase Ib dose-escalation and expansion study (NCT02203773), which is assessing the safety and efficacy of venetoclax in combination with decitabine or azacitidine in previously untreated older AML patients ≥ 60 years of age who are ineligible for standard induction therapy.

In this phase Ib study, oral venetoclax was co-administered at 400, 800, or 1200 mg daily with 20 mg/m^2 of decitabine on days 1–5 or 75 mg/m^2 of azacitidine on days 1–7, each 28-day cycle. Recently published data from this study demonstrated that venetoclax plus azacitidine or decitabine was "well tolerated" in newly diagnosed patients with AML who are unfit for standard chemotherapy with promising efficacy and low early mortality rate.[3] In addition, data presented at the 2018 American Society of Clinical Oncology meeting demonstrated that 400 mg of venetoclax has the optimal benefit-risk profile in combination with decitabine or azacitidine, which demonstrated a tolerable safety profile with deep

responses and durable outcomes in elderly patients with AML. Hence an expansion cohort followed patients treated with 400 mg venetoclax in combination with either HMAs or chemotherapy.[4] Daniel Pollyea presented the data from the expansion cohort.[5]

In the expansion cohort, 115 patients with AML (median age = 74 years; range, 65–86) received 400 mg venetoclax daily in a three-day ramp-up from 100–200–400 mg co-administered with azacitidine (n = 84; median age = 75 years) or decitabine (n = 31; median age = 72 years) on days 1–7 within each 28-day cycle.

Key findings:

- **Safety**
  - Most common grade ≥3 AEs across all patients were febrile neutropenia (44%), anemia (28%), pneumonia (25%), thrombocytopenia (22%) and neutropenia (18%)
  - ≤ 30-day mortality rate in patients receiving venetoclax plus azacitidine or decitabine respectively: 2% (2/84) and 7% (2/31)
- **Efficacy**
  - Data below is representative for responses in patients treated with venetoclax plus azacitidine or decitabine, respectively
    - CR/CRi rate: 71% (95% CI, 59–80%) and 74% (95% CI, 55–88%)
    - Median time to CR: 1.2 (range: 0.7–5.5) and 1.9 (range: 0.9–4.6)
    - Median duration of response after achieving CR/CRi: 21.2 months (95% CI, 14.4–30.2) and 15.0 (95% CI, 5.0–22.5)
    - Median overall survival (OS): 16.9 months (95% CI, 11.3–NR) and 16.2 months (95% CI, 9.1–27.8)
- Transfusion dependence for red blood cells or platelets within 8 weeks prior to venetoclax treatment was 64% (54/81) and 74% (23/31) in patients treated with venetoclax plus azacitidine and venetoclax plus decitabine, respectively
- MRD assessment demonstrated that 48% and 39% of patients with CR/CRi in the azacitidine and decitabine arm respectively, achieved MRD negative status (MRD negativity was defined as less than 10^{-3} leukemic cells at any measurement in bone marrow aspirates)

The speaker concluded by stating that the “venetoclax in combination with either azacitidine or decitabine led to high rates of rapid and deep responses that were durable in patients with AML ineligible for standard induction chemotherapy.” He further added that the findings of the study demonstrate that “venetoclax in combination with HMAs, may provide a potent therapeutic option for patients with AML who are not eligible for intensive chemotherapy.” Based on the findings of this study, a phase III study (NCT02993523) which is evaluating venetoclax 400 mg combined with azacitidine in adults with untreated AML ineligible for intensive chemotherapy is currently underway.

Venetoclax was recently approved by the US Food and Drug Administration (FDA) in combination with azacitidine, decitabine or LDAC for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude the use of intensive induction chemotherapy.

References

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