Acute myeloid leukemia

A LOW-TOXICITY THERAPEUTIC OPTION

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TRIAL SUMMARY: Preliminary safety and efficacy results with venetoclax in elderly patients

Wei A, Strickland SA, Roboz GJ, et al. Safety and efficacy of venetoclax plus low-dose cytarabine in treatment-naive patients aged ≥65 years with acute myeloid leukemia. ASH Annual Meeting, San Diego, California, December 3-6, 2016. Abstract 102.

This phase 1/2 study included older patients with previously untreated acute myeloid leukemia (AML) who were considered to be ineligible for induction chemotherapy, had Eastern Cooperative Oncology Group (ECOG) performance status 0–2, and adequate renal and liver function. Relevant exclusion criteria were acute promyelocytic leukemia, previous treatment with cytarabine, and central nervous system (CNS) involvement by AML. Patients were treated with 28-day cycles that included low dose cytarabine (low-dose cytarabine [LDAC], 20 mg/m^2 s.c. daily) on days 1–10 and venetoclax 600 mg orally daily on days 1–28 (days 2–28 after a 5-day dose ramp-up for the first cycle).

The 20 patients enrolled in the study had a median age of 74, and 8 had an antecedent hematologic disorder. Tumour lysis was not observed. The most common grade 3–4 adverse events were febrile neutropenia (35%), hypertension (20%) and hypophosphatemia (20%). Fourteen of 20 patients (70%) achieved a complete remission (CR) or complete remission with incomplete marrow recovery (CRi), with a median time to best response of 30 days (range 23–169 days). The 1-year overall survival (OS) estimate was 74.7% for all patients (95% CI, 49.4–88.6) and 86.7% for responders (95% CI, 56.4–96.5), with median OS not yet reached.

COMMENTARY: With a median age of onset approaching 70 years, AML is a disease of the elderly. While selected older adults might be eligible for intensive therapy (induction chemotherapy with or without allogeneic hematopoietic cell transplant), many will not be, and in this setting treatment options are limited. In addition to generally having unfavourable disease biology as compared to younger patients, older patients are more likely to experience treatment-related morbidity and mortality. Thus, the development of effective, low-toxicity therapeutic options for these patients is a priority. Beyond supportive care, single-agent low-dose cytarabine produces CR in a minority of patients (20%–30%) and marginally improves OS vs supportive care alone. The hypomethylating agents azacitidine and decitabine (only the former is available in Canada), have demonstrated similar activity to LDAC. However, azacitidine is likely more active than LDAC in patients with poor-risk cytogenetics and myelodysplasia-related changes, both relatively common in older patients with AML. Besides LDAC and hypomethylating agents, there are, unfortunately, no other available therapies for older adults ineligible for induction chemotherapy.

Venetoclax was recently approved by Health Canada for use in chronic lymphocytic leukemia, and is an orally bioavailable inhibitor of BCL2; an antiapoptotic protein known to be overexpressed in a number of malignancies. The use of this drug in AML was prompted by recent work demonstrating that BCL2 is overexpressed in leukemic stem cells. This study, along with a phase 1b study (presented at the American Society of Clinical Oncology [ASCO] meeting in 2016) examining venetoclax in combination with azacitidine or decitabine in the same patient population, have prompted the US Food and Drug Administration (FDA) to grant venetoclax breakthrough therapy designation for the treatment of AML in patients not eligible for induction chemotherapy. The findings of these studies are promising as they suggest that venetoclax, a convenient oral therapy, is associated with significant antileukemic activity with limited toxicity. These findings will be put to the test in a phase 3 randomized placebo-controlled trial that is set to open in early 2017 with an expected enrollment of 400 patients.

IN BRIEF

Already known
- Acute myeloid leukemia (AML) is a disease of the elderly, many of whom are not eligible for intensive therapy.
- Low-toxicity therapeutic options are a priority.

What this trial showed
- This phase 1/2 trial targeted older patients with untreated AML.
- In patients ineligible for induction chemotherapy, oral venetoclax showed significant antileukemic activity and limited toxicity.

Next steps
- A phase 3 randomized placebo-controlled trial starting in 2017 will test these early findings.