Combination Therapies Involving Gilteritinib and Venetoclax

Keith W. Pratz, MD
Assistant Professor of Oncology
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
Baltimore, Maryland

Welcome to *Managing AML*. I am Dr. Keith Pratz, and I am live at the ASH Annual Meeting in Atlanta, Georgia. Today I will be reviewing two clinical trial presentations: the first is the preliminary results of the phase 1 study of gilteritinib in patients with newly diagnosed acute myeloid leukemia, the second being an updated presentation on the safety and efficacy of venetoclax with decitabine or azacitidine in newly diagnosed, unfit AML patients.

Let us begin with the preliminary results of the phase 1 study of gilteritinib in combination with induction and consolidation chemotherapy in subjects with newly diagnosed acute myeloid leukemia.

This study involves the incorporation of a tyrosine kinase inhibitor targeting FLT3, which is one of the more common mutations in acute myeloid leukemia conferring poor overall outcomes, with standard induction chemotherapy of cytarabine and idarubicin. The study so far has accrued 50 patients since December of 2015. The background is that we are hopeful that the addition of a tyrosine kinase inhibitor to chemotherapy will improve the quality of remissions and overall survival in patients with this difficult-to-treat disease. The results that we will present show that patients achieved remission at a rate of 100% in patients with FLT3 leukemia in this small subset of patients. We had 21 patients with FLT3 mutations, most of which were ITD mutations; and 19 out of the 21 patients achieved a complete remission with full count recovery, and two other patients achieved complete remission with incomplete count recovery. Other patients on the study had various other mutations, none of which involved the FLT3 gene; but in those groups of patients, we had an overall response rate of 61%. The large majority of those patients had intermediate and adverse cytogenetic characteristics, and the results there are consistent with what you would see in the backbone of the therapy. The addition of gilteritinib did not appear to increase any of the toxicity, as we saw typical cytopenias and infectious complications with the regimen. The next step of this study will be further expansion at a higher dose. We have done correlative studies as part of this study so far, and we believe we are nearing the dose where we think will achieve complete inhibition of FLT3, which in previous studies have been associated with favorable outcomes in this subset of patients. After the expansion cohorts are complete, we anticipate a randomized phase 3 study to establish the overall efficacy of gilteritinib in this patient population. For community practitioners, we are expecting one of the second-generation FLT3-targeted agents to become available in the next year or two; and we are expecting that this will create other options for patients with FLT3 disease beyond midostaurin, which is on the market currently.

The second abstract which we will present today is the safety and efficacy update of venetoclax with decitabine or azacitidine in treatment-naïve elderly patients with acute myeloid leukemia.

Venetoclax is an oral BCL-2 inhibitor that has been approved for use in relapsed and refractory chronic lymphocytic leukemia. This study is incorporating it into a low-intensity therapy involving one of the two demethylating agents for patients with newly diagnosed acute myeloid leukemia who are otherwise unfit for cytotoxic chemotherapy. The background of the study is that initially 50 patients were accrued in the dose escalation portion of the study, and 100 additional patients were studied in an expansion phase. The report will review the outcomes in both sets of those patients. The results of the study showed that this was a group of patients typical for an elderly population, with a median age of 74 years. We treated 145 patients, with 49% of those patients having poor-risk cytogenetics and 51% of those patients having intermediate-risk cytogenetics. Adverse events were typical with those seen with hypomethylating agents, most of which were cytopenias and infectious complications. Tolerability of venetoclax was excellent as we had very few patients discontinued for side effects related to the study drug. The objective response rate in complete remission and incomplete count recovery rate in the 145 eligible patients was 67%, with 30% of those patients having complete remission with full count recovery and 37% of those patients having complete remission with incomplete count recovery. Broken down by cytogenetic risk categories: 74% of patients who had an intermediate risk karyotype achieved response, and 60% of patients in the poor-risk cytogenetic subgroup achieved complete response or complete response with incomplete count recovery. The median time of response was 11.3 months in all patients on study, and the median overall survival was 17.5 months. The next steps of development of this combination involve the incorporation of venetoclax into an azacitidine backbone and a randomized placebo-controlled phase 3 study, currently enrolling in the United States and overseas. We are very optimistic with this combination and we expect this will open options for patients who are otherwise unfit for hospitalized care for their acute myeloid leukemia in the difficult-to-treat subset.

Thank you for viewing this activity.

References:

Pratz K, Cherry M, Altman JK, et al. Preliminary Results from a Phase 1 Study of Gilteritinib in Combination with Induction and Consolidation Chemotherapy in Subjects with Newly Diagnosed Acute Myeloid Leukemia (AML). *Blood.* 2017;130. Abstract 722.

DiNardo CD, Pollyea DA, Jonas BA, et al. Updated Safety and Efficacy of Venetoclax with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients with Acute Myeloid Leukemia. *ASH 2017*. Abstract 2628.