ManagingAML

Chapter 1: Combination Therapy with Novel Agents and Chemotherapy Improves Survival in Diverse Subsets of AML Patients

Naval Daver, MD
Assistant Professor
Department of Leukemia
The University of Texas
MD Anderson Cancer Center
Houston, Texas

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

Nivolumab-AZA Combination Therapy Improves Stable Disease in Relapsed AML (S474) – Naval Daver, MD

Welcome to *Managing AML*. My name is Dr. Naval Daver, and I am an Assistant Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer in Houston, Texas. Today, I will be reviewing a phase 1B/2 study of nivolumab in combination with azacitidine in patients with relapsed AML. This was a study that we began about two years ago at MD Anderson. We had done, before starting this study, immune expression data on about 100 AML patients. What we saw is that in AML T-cells, including total CD3 as well as CD8 population, there was overexpression of PD1. This was seen at a high level in relapsed AML as compared to new AML, but both relapse and new AML had a higher expression in healthy donor bone marrow aspirates. Also, we had done some preclinical work with azacitidine with other physicians in our group including Dr. Garcia-Manero, and we had shown that azacitidine upregulates specifically PD1 on T-cells and PDL2 and PDL1 on the AML blasts. This formed the rationale for doing the combination of azacitidine with the PD1 and PDL1 inhibitor. The study that was initiated was a phase 1B, phase 2 study and we had an initial dose-finding period for the first six patients where we gave them the standard dose of azacitidine 75/m^2 and nivolumab 3 mg/kg, day 1 and 14. The study was found to be safe in the first six patients, so then we expanded to 70 patients in total. Overall, the response rate that we saw looking at the IWG AML response criteria was about 33% to 35%. Interestingly, we did have a subset of patients who had stable disease or hematological improvement. This was seen in about 10 patients and in most cases was durable beyond 6 months. In fact, we have had some stable disease in hematological improvement, specifically four patients who have maintained this for more than one year without transplant. This is interesting and has been well-defined in immune checkpoint treatments in lymphoma, myeloma, and solid tumors that less than achievement of a complete remission may actually still be associated with a clinical benefit and improved survival. We need to explore these additional responses, especially when we are looking at the immune checkpoint or some of the newer HMA-based treatments.

What we also saw that was interesting was that the overall survival in the salvage AML group was seven months, which has been better than the survival we have achieved with azacitidine or decitabine alone in salvage AML population at our institution when we reviewed a historical cohort of match patients. Furthermore, in salvage 1 especially, patients who had older phenotype and who had failed prior treatment, we had a median overall survival of 10 months with almost 50% alive at two years, and this was after censoring for transplant. These results to us were very encouraging, and we believe that this study will now be evaluable in the frontline, and we have started the frontline cohort. Also, what we did was we looked at T-cell profiling and

expression, and we did find biomarkers, specifically, that people who had more CD3 positive T-cells in their bone marrow aspirate and more CD8 positive T-cells in their bone marrow aspirate had a much higher chance of achieving a response as well as survival, almost in the range of 70%, as opposed to those who had low T-cell infiltrate in the bone marrow to begin with. They had a much lower chance of response of 15% to 20%. Also on treatment, we saw that there was upregulation of immune activation markers in the bone marrow aspirate in responders. This was not seen in the non-responders, indicating that the clinical response went along with development of an immunological response in the bone marrow Furthermore, we saw that CTLA4 was upregulated, more specifically, in non-responders as opposed to responders, indicating this could be a major immune counter regulatory checkpoint pathway of resistance and the combination approach could further improve response rate. We are now embarking on the combination of nivolumab, ipilimumab, plus azacitidine, both in salvage AML as well as in the frontline AML setting.

We think that these studies could be very complementary to a lot of the molecular data that is emerging in AML with venetoclax, IDH, FLT3, and could eventually be a role for combining these agents since they act through different pathways, have different toxicities, and could really improve the future of AML, just as we have seen with triplet and quadruplet combinations in myeloma.

Outpatient Azacitidine-based Chemotherapy Combined with BCL-2 Suppressing Agent Induces Durable Deep Remissions in AML (S472) – Keith W. Pratz, MD

My name is Dr. Keith Pratz. I am an Assistant Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University in Baltimore, Maryland. Today, I will be reviewing the results of data which looked at the safety and efficacy of venetoclax in combination with decitabine or azacitidine in treatment-naïve elderly patients over age 65 with acute myeloid leukemia (AML). The background of this study is the combination of venetoclax and decitabine or azacitidine has been examined in a dose escalation study which showed promising early activity. In our presentation here at EHA, we will review the 100 patients treated on the expansion cohort. Venetoclax is a targeted agent which suppresses BCL2 which is commonly overexpressed in acute myeloid leukemia preventing apoptosis. The blockage of BCL2 with venetoclax leads to release of proapoptotic proteins resulting in increased cell death in combination with these demethylating agents. The results of this study showed a very high level of clinical responses in patients who have never been treated for acute myeloid leukemia. The combination showed an overall response rate of 68% either as a complete remission or complete remission with incomplete count recovery, and the duration of these responses seem to be long-term. We have not reached our median overall response time as of yet. Our estimates of survival show 79% are alive at 6 months and 70% are alive at 1 year post initiation of therapy. The tolerance of this combination seems to be quite good. The hospitalized care is only provided for the first 3 to 4 days as treatment is initiated. The rest of the combination of therapy will be given as an outpatient. Side effects are typical of those given the background disease including neutropenic fevers, neutropenia, thrombocytopenia, and anemia. Patients have adhered to the scheduling except for times of cytopenias. Approximately 35% of patients after cycle 1 required dosing delays due to persistent cytopenias. The next steps to this combination include examination in a phase 3 study where the dose of venetoclax will be left at 400 mg daily and the backbone hypomethylating agent will be azacitidine. The overall response

rates, the durations of response, and the overall tolerance of this combination seem to be quite good in this hard to manage patient cohort. We anticipate a benefit in overall response over azacitidine alone in this phase 3 study. The key points to take away from this are that outpatient styled azacitidine-based chemotherapy can induce durable deep remissions for acute myeloid leukemia when given in combination with a BCL2 suppressing agent such as venetoclax. The remaining challenges will be to see if the study outcome seen in the university treatment population will hold true in a larger group of patients in community practices.