What is standard of care for patients unfit for intensive induction chemotherapy, and what is under investigation?

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Welcome to *Managing AML*, I am Dr. Naval Daver. I will be discussing current standard of care for patients who are unfit for intensive chemotherapy, as well as novel agents under investigation for patients who fit into that "unfit for induction" category. At this time, there has been significant progress in patients above the age of 65 years with acute myeloid leukemia, with the advent of a number of new agents coming forward for this population. The standard therapy for acute myeloid leukemia had been induction chemotherapy, which is usually based on a backbone of anthracycline with cytarabine. The most common version of this is the 3+7 regimen used widely across the United States, but there are other variations of this, such as FLAG-IDA, CLIA, CICA, or CLAG-M. The goal of all of these induction-based regimens is to achieve what we call a complete remission, meaning getting the bone marrow blasts below 5% with the recovery of neutrophil and platelet count, as there is significant data suggesting that this is associated with improved survival. One of the issues that we have noticed is that, although these induction regimens are quite effective in achieving complete remission rates (with complete remissions in the range of 70% to 85%), they do have significant cytotoxicity such as infections, fever, mucositis, and diarrhea. In the past, when we have tried to use these regimens in patients above 65, especially in patients above 70, we have encountered significant induction-related toxicity, severe infections, and mortality rates of 20% to 40%. Because of this, there has been a huge shift in the last 8 to 10 years to try less intensive and noncytotoxic-based therapies for patients with AML who are considered unfit for induction.

The definition of who is unfit for induction is not clear and there have been different publications looking at different factors. In general, we consider patients who are above 65, especially those above 70 years of age, a population that should be considered for non-intensive chemotherapy. Additionally, patients who are above 60 years of age but may have other adverse features such as comorbidities; poor performance status; cardiac, liver or kidney disorders; or complex cytogenetics or mutations such as TP53, traditionally do not tolerate induction chemo well and/or may not respond well to induction chemotherapy. This would be another population where we would use non-induction-based treatments.

The most common drugs that have been used in the non-cytotoxic induction-based arena are azacitidine and decitabine, both of which have gone through phase 3 trials. The azacitidine was used in a phase 3 trial of azacitidine versus standard of care in Europe and was published in *Blood* a couple of years ago. They showed that the use of azacitidine, when compared with

standard of care treatment such as low-dose cytarabine or hydroxyurea-based supportive care, resulted in improvement in response rate, with response rates of 30% to 35%; and improvement in median overall survival, with a median overall survival of 11 months. A similar phase 3 was done that looked at decitabine versus standard of care, which included hydroxyurea best supportive care or low-dose Ara-C. It was shown that, again, decitabine was able to significantly improve the median overall survival as well as the response rate. Both azacitidine and decitabine, in addition to improving response rate and overall survival, had a very low induction mortality in the range of 4% to 7%, which is much lower than we were used to seeing with induction-based treatments where the induction mortality was 25% to 40%. This has established azacitidine and decitabine as standard frontline treatments for elderly patients, usually those above 65 or 70, and also for patients who have other comorbidities and may not tolerate induction-based treatments.

Recent data also seems to suggest that decitabine, especially when given as a prolonged 10-day version of decitabine, seems to have a favorable impact and improved response rate, as well as a trend for improved survival in patients with TP53 mutations and adverse cytogenetics. This data was based on a single-arm study from the University of Washington and is being evaluated further in randomized fashion, but could be a consideration if you have a patient with a TP53 or complex cytogenetic, especially if they are above 60 years of age.

Now in the past four to five years, there has been further development in the use of azacitidine or decitabine. There are three main drug categories that are being added to azacitidine or decitabine to further improve the response rate. One of them is the drug venetoclax, a BCL-2 inhibitor. Venetoclax was initially evaluated as a single agent in relapsed AML patients where it showed a moderate response rate of 19%. However, it was subsequently evaluated in a phase 2 study in the front-line setting in elderly patients not fit for intensive chemo; 160 patients have been treated now in this expanded phase 2 as of the last update that was given at ASH 2017. The response rate has been very striking with the combination of azacitidine and venetoclax giving a complete response (or a complete response with incomplete count recovery) of 75%. This is much higher than the 30% response rate that we are used to seeing with azacitidine or decitabine alone in elderly front-line AML. More interestingly, the median overall survival is also doubled with the azacitidine and venetoclax as compared to what we get with azacitidine and decitabine alone; and the two-year survival in all patients who were treated on this combination (160 as of the last update) was 50%. This is the first time we are seeing prolonged survival of 50% or more in elderly AML. Historically we would have 15% to 20% of patients with long survival. We think this is going to be a major breakthrough for treatment of elderly and unfit AML, but it may also start being used also in younger AML populations, as there are a number of trials now combining venetoclax with many different treatments.

The other two agents that are of interest here are IDH inhibitors and FLT3 inhibitors. There have been phase 2 studies showing that the addition of FLT3 inhibitors such as sorafenib, quizartinib, or gilteritinib to azacitidine may significantly improve the response rate in FLT3-

mutated elderly patients over azacitidine alone, with response rates in the range of 70% to 80%, which are much higher than 30% expected with azacitidine. Similar efforts are being looked at with an IDH inhibitor added to azacitidine or decitabine where early data again presented at ASH 2017 seems to suggest that there may be an improvement in response rate. I think we are now getting into a situation where we may be able to get overall remission rates of up to 70% to 75% across the board in patients who are traditionally considered unfit for induction chemotherapy. This is very encouraging because these response rates are actually comparable to response rates we get with standard induction chemo with $1/5^{th}$ or $1/6^{th}$ the induction mortality rates. This could allow us to have all our elderly AML patients exposed to treatment and, as it looks at this time, 50% of them may have a chance of long-term survival, which is very encouraging.