Chapter 4: Improved Efficacy, Safety with CPX-351 in Older Adults with Newly Diagnosed Therapy Related AML

Jorge E. Cortes, MD
Deputy Chair and Chair
Chronic and Acute Myelogenous Leukemia Sections
Department of Leukemia
The University of Texas, MD Anderson Cancer Center
Houston, Texas

Overall Survival with CPX-351 versus 7+3 in Older Adults with Newly Diagnosed, Therapy-related Acute Myeloid Leukemia (P556)

My name is Jorge Cortes. I am the Deputy Department Chair in the Department of Leukemia at the MD Anderson Cancer Center in Houston, and I am also the Section Chief of AML and CML Sections there. Today, I will be reviewing from the European Hematology Association Meeting in 2017 in Madrid, Spain, the data from the trial which looked at the overall survival with CPX 351 versus 7+3 in older adults with newly diagnosed therapy related AML, and this is a subgroup analysis of a phase 3 study. The background of this study, first I will describe the drug, CPX-351 which is the experimental drug here. It is a liposomal formulation that encapsulates daunorubicin and cytarabine and keeps it at 5:1 molar ratio of cytarabine to daunorubicin. This is important because it has been identified that this is the optimum molar ratio that improves the killing of the leukemic cells and the liposomal encapsulation in addition to keeping that molar ratio, more specifically directs the active drugs into the bone marrow cells, specifically the blasts. In animal models, it has been shown to be significantly more active than the free compounds of cytarabine and daunorubicin. Early studies have shown that it is very active, and then earlier phase 2 randomized studies suggested that there were benefit compared to standard therapy. That led to a large phase 3 randomized trial, a pivotal trial, where patients age 60 to 75 with newly diagnosed AML but secondary, secondary to either prior therapy from other cancers or secondary evolving from myelodysplastic syndrome, were randomized to receive either the CPX-351 or 7+3. The overall result of that study where the primary endpoint was overall survival was positive. There was about a 50% improvement in the overall survival of these patients of the total population with a median survival of a little over 9-1/2 months compared to 6 months with the standard therapy. Significantly more patients alive at 2 years, for example, about 30% with the CPX-351 versus only about 12% with the 7+3. That is the overall study, and what the study that we are discussing today represents is the subset specifically of patients with therapy-related acute myeloid leukemias. I mentioned earlier both these patients and patients with AML secondary to MDS were included, but we recognize that these two populations, although we call them both secondary, may not have the same outcome.

It was important to check what the outcome was specifically of these subsets of patients. Approximately 20% of all patients in the global study were in this category of patients with therapy-related acute myeloid leukemia. There was a balance between the two arms (between the CPX-351 arm and the 7+3) about 30 on each one of the two arms, and the patient characteristics were also very balanced. This was targeting patients over the age of 60, so they are all in that age category, and all the features were balanced. There was a little bit of

imbalance in the type of prior therapy that they had received. For example, there were a few more patients that had received only radiation therapy for whatever their prior cancer was in the CPX arm, but there were also more patients that had received non-anthracycline chemotherapy plus an anthracycline-containing chemotherapy plus radiotherapy in the CPX 351, so generally they were balanced, although a few distributions of subsets were a little different. Because the primary endpoint of the whole study was overall survival, the first thing that we looked at in these subset analyses was the overall survival. In keeping with the overall results of a general study, the median survival for this patient population was also significantly better for the CPX-351 group versus the 7+3 group. The median survival was 12.17 for the CPX group and 5.95 for the 7+3 group. A doubling of a median survival with a hazard ratio of 0.49 is statistically significant, and those curves do not merge. They continue being separated up to two years which is about the followup that we have on the study. That of course correlated with an improvement in the response rate when we look at both CR and CRI. The response rate was 47% for the CPX arm and 36% for the 7+3 arm. That also contributed to the fact that more patients proceeded to transplant in the CPX arm (37%) than on the 7+3 arm (27%). Now, when we do different analyses of survival censoring for transplant and other things, the CPX arm stays above, whether you account for transplant censoring or not. In all these measures of success, the CPX arm turned out to be significantly better in this subset of patients with therapy-related acute myeloid leukemia.

Now, in terms of safety as for the general study, the safety was very comparable between the two arms. One important measure of safety is the early mortality. We looked at it both at the 30 days and the 60 days, and both were actually lower in the CPX 351 than in the 7+3. At 60 days, for example, it was 13% versus 25%, so almost half the early mortality with the CPX-351 arm. There was a little bit more prolonged myelosuppression with the CPX, but again it did not result in more deaths. There were a few adverse events that were more common with CPX, like rash and headaches, but none of the serious adverse events were more common with CPX-351. Overall, the safety profile was equivalent or if anything, particularly looking at the early mortality, better with the CPX-351. These are the results, and so the question then is what does this mean in terms of the treatment landscape of AML? Well, the drug CPX is still experimental, although it is being evaluated by the regulatory authorities, and we expect that we will hopefully see approved in the near future. I think with these results this would become the new treatment standard for these secondary leukemia patients, whether they are in the treatment-related category or in those that are evolving from a myelodysplastic syndrome or that have myelodysplastic features in the bone marrow, and because the drug is safer, there are no concerns about trading efficacy for safety. It looks like we have gained in both categories of efficacy and safety. I think that what this tells us is that even when we are talking about the same active compound, cytarabine and daunorubicin, a better delivery, a better formulation could significantly improve the outcome of patients, and that perhaps is a message for other chemotherapeutic agents that we use in other cancers. It will be interesting to know, for example, what happens with putting other duplets in a similar formulation that are commonly used in other cancers, or can you include in this liposomal formulation more than two drugs because in some diseases we use more than two drugs? There are important additional steps that could be done to take this methodology further. We could ask, because daunorubicin and cytarabine are used not only in secondary AML, but we use it in younger patients with AML and de novo AML, etc., would it be better than using 3+7 in those other categories? That has not

been done and that has not been tested, but that will be an important question to ask in future studies. I think that there is excitement about these drugs, the potential that we could use it for these patients with secondary AML improving our efficacy, improving our safety profile. A lot of work has to be done to see if it could be expanded further into other categories. With this, I conclude my presentation, and I thank you for viewing this activity.