Emerging Combinations and Therapies in Newly Diagnosed and Relapsed/Refractory AML

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Welcome to *Managing AML*, I am Jorge Cortes. I will be reviewing two abstracts that we presented at the European Hematology Association in 2018 Annual Congress in Stockholm, Sweden. First, I will review the outcomes by number of induction cycles with CPX-351 versus 7+3 chemotherapy in older adults with newly diagnosed, high-risk/secondary acute myeloid leukemia, then I will discuss the phase 1 dose escalation study of the IDH1m inhibitor, FT-2102, in patients with AML or MDS.

Let's start with the first abstract, and this is the randomized study of CPX-351 versus 7+3. As a reminder, CPX-351 is a liposomal encapsulated combination of daunorubicin and cytarabine on a molar ratio that is a constant of 5:1 (5 of cytarabine to 1 of daunorubicin), and that has been shown in preclinical studies to be the optimum molar ratio. It's maintained throughout the infusion and the life of the drug, not only in circulation but also in the bone marrow, and that increases the killing of the leukemia cells in animal models, resulting in prolonged survival. Some randomized phase 2 studies suggested that there was a benefit for this drug compared to standard therapy both in the frontline and in the salvage setting, and showed that perhaps the patients that had the most benefit were those with secondary leukemias. That led to this pivotal trial that was for older patients ages 60 to 75 with newly diagnosed, high-risk, or secondary AML (either treatment-related AML or with a history of myelodysplastic syndrome). That study demonstrated a survival benefit for patients treated with CPX-351.

In this abstract what we did was an exploratory analysis to determine the outcome of patients who received either one induction cycle or two induction cycles. The design of the study allowed for patients randomized to either one of the two arms to receive a second cycle of induction based on the outcome of a bone marrow that was planned for day 14. If that showed persistent leukemia, the investigators could consider giving a second cycle of whatever the treatment that the patients were randomized to. In addition to the analysis of the survival, the secondary important outcome measure of success was the response rate; either complete remission or complete remission with incomplete platelet recovery or incomplete neutrophil recovery (CRi). Then patients could receive up to two consolidation cycles, but again this analysis that I'm talking about today relates mostly to the outcome after one or two induction cycles of chemotherapy.

Overall, this study included 304 patients; CPX-351 had 153 patients and 3+7 had 151. The study was well-balanced in the characteristics of the patients. Remember, these were patients age 60 to 75. When you look at the patients that received one induction cycle only versus two induction cycles, the balance remains. Perhaps, if anything, there were a little bit more of the older patients in the second induction cycle with the CPX-351, which speaks to the fact that this drug is very well-tolerated, even in this older patient population. Importantly, going to the core of the results of this study, there were more patients treated with CPX-351 that achieved remission with only one induction cycle compared to patients that received 3+7. With the CPX-351, after one cycle of chemotherapy, 55% of patients achieved a CR or a CRi (45% had a CR), compared to 34% of patients that had an overall response (28% CRs; the rest were CRi's). That already speaks to the benefit of CPX-351 because as we know achieving a remission with one cycle carries a better outcome.

For the second cycle of chemotherapy, fewer patients, of course, proportionally required the second cycle in the CPX arm because more patients had responded to the first cycle. There was no difference in the response rate among the patients who received the second cycle; it was overall a response rate of 31% with CPX, 35% with 3+7. The CR rate was 21% and 24% respectively. One important thing is that there was a greater proportion of patients that achieved a remission after one cycle that went to transplant, compared to patients that achieved the remission with 3+7. Some of that may have been related to the fact that these patients not only responded, which is a criteria for the transplant, but also were able to tolerate this treatment very well. We did see in the pivotal trial, and in this sub-analysis it is confirmed, that the tolerability of CPX-351 is at least as good as that of 3+7, if not better, in some aspects. There is a slightly more prolonged myelosuppression, but other than that, no significant difference in adverse events. In this abstract, we looked at the frequency of adverse events by cycle. For example, the frequency of grade 3 to 5 treatment-emergent adverse events was very similar between the two arms. Overall, 71% of patients with CPX had any treatment-emergent adverse events grade 3 to 5, and 74% of patients in the controlled arm of the 3+7. Interestingly enough, among the patients who received the second cycle of induction of CPX-351 had a lower rate of adverse events grade 3 to 5; it was only 79% compared to 94% with the 3+7, again speaking for the good tolerability. As you can imagine, the most common adverse event for grade 3 to 5 in both arms was neutropenic fever.

I think these results overall confirm the benefit of CPX-351 in this population that has very poor prognosis with secondary AML, treatment-related AML, or secondary after myelodysplastic syndrome. It is very well-tolerated among this patient population ages 60 to 75, but importantly you can achieve a higher rate of remissions with only one cycle of induction chemotherapy with CPX-351. That results in a higher proportion of patients being able to go to transplant after only one cycle. Even just comparing the patients that get a remission with one cycle, still more patients go to transplant if they receive CPX-351, and the treatment is associated with a safety profile that is at least equivalent and perhaps better (it certainly looks like that in the second

cycle of induction). Overall, this underscores the benefit of this drug that is now approved, and we use it regularly for these patients with secondary acute myeloid leukemias.

I'm going to move now to the second abstract. This second abstract relates to this new drug which is FT-2102, an IDH1 inhibitor. As a reminder, IDH mutations – specifically IDH1 mutations – occur in about 7% to 14% of patients with AML and in a much lower percentage of patients with MDS, only 3%. As you know, there is also an IDH2 mutation that occurs in a similar percentage of patients. These two mutations are almost mutually exclusive; patients tend to have one or the other. Importantly, the mutation changes the metabolism; if you remember the Krebs cycle, the IDH1, what it does when it's mutated is it converts the alpha-ketoglutarate into 2-hydroxoglutarate. It's important because this 2-hydroxyglutarate or 2HG has a pro-leukemic effect probably through epigenetic mechanisms. Patients that have these mutations have elevated levels of the 2HG. The mutation doesn't necessarily have a poor prognosis but it has become an important target for therapy, and FT-2102 is a very potent and selective small molecule inhibitor of IDH1. As you know, there is a drug that was recently approved that's also an IDH1 inhibitor (ivosidenib). In addition to the high potency, other benefits of this drug, FT-2102, is that it does not have any potential for QTc prolongation and it also does not induce its own metabolism. With some of the other drugs that have been investigated, the plasma levels decline over time; whereas it was anticipated from preclinical work that that would not happen with FT-2102, and I'll get back to that in a minute.

What I'm talking about today is this poster that we presented at EHA where we are reporting the results of a phase 1/2 study evaluating the safety, the pharmacokinetics/ pharmacodynamics, and the clinical activity of this inhibitor. In this study we have both arms that explore it as a single agent alone or in combination with azacitidine for patients with AML or MDS. The design is a typical 3+3 dose escalation defining the maximum tolerated dose (or a minimum effective dose) in both the single-agent and the combination setting, and then there are multiple expansion cohorts underway. The doses that have been evaluated are 150 mg every day both as a single agent and in combination, 300 mg every day only as a single agent, and 150 mg twice a day both as a single agent and in combination.

The response criteria are the standard definitions for the IWG and assessed by the investigator. There is no central review at this point. The poster presented 35 patients that were evaluable at that point. They received a median of two prior treatments, so this was a heavily pretreated patient population; they had refractory or relapse disease, all of them. At the time of this analysis, almost half of the patients remained on study. Sixteen patients remained – ten on the single agent cohort, six on the combination cohort – and have received a median of two treatment cycles. Some of the discontinuations have been patients who responded and then proceeded to a stem cell transplant, which is what we tend to do in patients with refractory or relapse disease.

The drug has been extremely well-tolerated. Very few adverse events; treatment-emergent adverse events, the most common ones are fatigue and nausea and febrile neutropenia. Really, mostly things that we see typical of the diagnosis itself of acute myeloid leukemia. Very few adverse events that are grade 3 or 4 and very few that were considered related to the study drug. Grade 3 or 4, the most common ones are febrile neutropenia, anemia, pneumonia; again, things that we expect with patients with leukemia. Importantly, one of the things that we know that occurs with both IDH1 and IDH2 inhibitors, and that is common to all of the drugs that have been investigated in this setting, is differentiation syndrome. We know that in some patients there could be an increase in the white cell count and the blast count, and it's also associated with fluid retention, cough, peripheral edema, hypoxia; very similar to what you see with an ATRA differentiation syndrome. It can be managed with treatment interruption, with corticosteroids, with diuretics. This happened at grade 3 in 14% of the patients so far. It is manageable with interventions, with diuretics and corticosteroids as I mentioned and sometimes with interruption of the drug. It did not result in permanent treatment discontinuation in any of these patients, so it's just important to know about differentiation syndrome and stop therapy when it's indicated.

There was a very good response rate and the pharmacokinetics are very favorable. Number one is that the concentrations that are achieved at the dose of 150 mg b.i.d., which is the dose that is being carried forward, achieved plasma concentrations that exceed the IC-90 for inhibition of the mutated enzyme. Importantly, those levels remain throughout – beyond five cycles of chemotherapy. We have data up to seven cycles and those plasma concentrations do not decline. As I mentioned, this is one of the benefits of this drug. Another thing is that the concentrations of the 2HG declined very rapidly and they reached normal concentrations by the start of cycle two. Patients keep that 2HG to normal levels. In conjunction with the sustained plasma levels of the drug, we see that the concentrations of 2HG remain normal throughout the therapy, and that's an important biomarker of the efficacy of the drug.

In the single agent, the response included two patients that achieved a complete remission, four patients that have achieved a CRi, and five patients that have had some clinical benefit, a stable disease. Two patients had significant improvement in the blast count that may not reach the criteria for CR, but at least a 50% decline in the blast count. Now, it's important to underscore that with treatment with this drug, the responses may be delayed. These stable diseases are beneficial, and we have seen that with some of the patients that have been on treatment longer, their response improves with time to a CRi and then to a CR. It is very important that these patients remain on therapy even when you don't get a complete remission in the first cycle. This is not like chemotherapy where you do expect remission in the first or second cycle. In the combination arm, we also have seen very good responses. We have fewer patients – eleven evaluable – but we have two patients with a CR, one with a CRi, and five with a clinical benefit. The majority of patients have had at least some clinical benefit and the combination has been extremely well-tolerated.

In conclusion, I think that this agent, FT-2102, is a very attractive drug that is very safe, has very few adverse events, has very good pharmacokinetic and pharmacodynamic properties that make it useful for prolonged use which is what you will need for a drug like this. It has already shown significant activity, even at these early stages, in patients with IDH1 mutated AML or MDS that have been refractory to prior therapy, both as a single agent with a 38% response rate (and higher if we include the stable diseases and clinical benefit), and 27% in the combination with azacitidine (again much higher if you include those patients that are still in therapy with stable disease). This study has been expanded. There are multiple cohorts that are being added to this study including evaluation after transplant, evaluation in patients who have received other IDH1 inhibitors, and several other cohorts to see the whole spectrum of potential uses for this drug. With this, I will end the presentation. Thank you for your attention.

Abstracts

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