CPX-351 vs 7+3 in Older Adults: Efficacy and Safety Reported in Clinical Trial

Jeffrey E. Lancet, MD
Department Chair
Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

Hi, my name is Dr. Jeff Lancet. I am from the Moffitt Cancer Center in Tampa, Florida, and I am live at the ASH Annual Meeting in Atlanta, Georgia. Today I will be reviewing data on the efficacy and safety of CPX-351 versus 7+3 in older adults with secondary AML.

Just as a bit of background, CPX-351 is a liposome that encapsulates two commonly used chemotherapy drugs, daunorubicin and cytarabine, in a fixed molar concentration ratio of 5:1 of cytarabine to daunorubicin. The beauty of this model is that it is a unique delivery vehicle such that two different drugs, namely daunorubicin and cytarabine, can be delivered to the leukemia cell or other cell of interest at a specified and optimal synergistic ratio; and this is not really something that can be achieved with free-drug administration. It is really a novel delivery system to take advantage of synergistic activity between two known and established chemotherapy drugs for acute myeloid leukemia. This particular drug has been developed over the course of several years, first through a phase 1 trial that demonstrated safety and intriguing signals of efficacy in the relapsed/refractory population of patients with primarily AML. It demonstrated that the drug itself was associated with a very prolonged plasma exposure; for up to a week after the final administration of the drug, you could still detect circulating levels of daunorubicin and cytarabine, which was an interesting finding. In addition, you could actually maintain the molar ratio of 5:1 for several days after the drug was administered; so the drug was being maintained in the specified and desired molar ratio after being administered.

That is a bit of a background on CPX-351 in the phase 1 trial. This led to a phase 2 trial that subsequently demonstrated improvement in overall response rate in older patients with newly diagnosed AML, with a signal of improved overall survival, again in older patients but with secondary AML. A subset of patients who were older that had secondary AML was the group that was detected to have what seemed to be a survival advantage with CPX-351, compared to conventional 7+3 chemotherapy in this randomized phase 2 study. After all of that, a randomized phase 3 trial was undertaken, again comparing CPX-351 against standard 7+3 (daunorubicin plus cytarabine). This was in a prospective phase 3 randomized setting, again, in patients who were over age 60, but focusing on the patients with high risk or secondary AML, namely patients with AML with MDS-related changes such as patients that had a prior history of MDS or cytogenetic changes associated with MDS. We also included patients that had therapy-related AML, as defined by having received some type of systemic cytotoxic chemotherapy for a prior cancer. We presented the original results a year ago that revealed an overall survival advantage for patients who had received CPX-351 compared to those that had received 7+3.

This phase 3 trial eventually led to the ultimate approval of CPX-351 by the US FDA a few months ago and is now considered a reasonable drug to be used with an indication as first-line therapy in older, fit patients, or any fit patient with secondary or otherwise high-risk AML.
In this particular analysis that is being presented at the current ASH Meeting, we basically expanded upon our experience by combining the population of patients who had been treated on the phase 3 trial, but now included patients who were also treated on the phase 2 trial that had secondary AML. Basically we were combining patients with secondary AML from the phase 2 trial and the phase 3 trial to really expand the experience and understanding of how well this drug worked in patients with this poor-risk phenotype. This analysis added about 50 or so patients to the overall population of what was studied in the phase 3 trial to lend some confirmatory data to the overall outcomes, and to make sure that the data were holding up through a larger group of patients. What we found was that indeed when we included the patients from the phase 2 trial in this combined analysis that the data were very similar to what was observed in the phase 3 trial. There was a significant overall survival advantage that was detected at one year in favor of the CPX-351-treated patients compared to the 7+3-treated patients. There was an overall response rate including CR and CRi that was about 48% in the CPX arm compared to about 33% in the 7+3 arm. This was similar to what we found in the phase 3 trial, so the data are holding up on this expanded analysis as well. We also noted that patients that had gone to allogeneic transplant, again in this expanded analysis, had better outcomes following initial treatment with CPX-351 compared to initial treatment with 7+3. This overall analysis gave us more confidence that the treatment of CPX-351 was really holding up amongst a larger cohort of patients; a group of patients that traditionally does quite poorly with induction chemotherapy based on the knowledge that secondary AML is associated with a very poor outcome and typically not very responsive to traditional chemotherapy. This particular analysis confirmed many of the findings that we saw in the phase 3 trial.

Yet it is not a perfect drug and there are still many patients that will not respond to CPX-351, or patients that will relapse. We have to keep in mind that there is a lot of work to do to improve the outcomes of these patients ultimately, and that is an important point moving forward. I see some of the challenges with respect to CPX-351 reflecting the fact that we do not yet have a full and comprehensive understanding of how the drug is working, what particular subsets of patients within the high-risk or secondary AML population are truly benefiting from this drug, or of those patients that are not experiencing any benefit from the drug. I believe that some of these data will be highlighted over the next several months as we learn more about the molecular profiling of patients pre- and post-treatment to better understand what molecular subtypes or mutational profiles are associated with poor outcomes, and what types of mutational profiles at the time of transplant may be associated with better outcome that could explain the beneficial effect of CPX-351 in the transplant of patients. Certainly, the ultimate challenge is how do we use this drug in combination with other agents to ultimately improve the outcomes of these patients? AML is a very complex disease with many different overlapping and non-overlapping biological pathways and signaling pathways that create resistance, so we need to understand how to combine this type of chemotherapeutic drug with other drugs that

are also active in AML to ultimately improve the outcomes, response rates, and survival of patients with high-risk AML.

In terms of next steps, there are several steps that can be taken. As I mentioned, combining CPX-351 with novel agents is an important step moving forward; and I believe that you will be hearing about and seeing reports of new trials that are combining CPX with other agents in the near future. These agents may include such things as FLT3 inhibitors, IDH inhibitors, and others that may very well have a role in treating the high-risk patient population. As I mentioned, I think that with respect to this particular trial, we will be learning more about the molecular profiling of patients who responded and who did not respond that will guide us in terms of identifying the most appropriate patients for CPX in the future.

Now as a practicing physician, it is important to know how to use the drug and some of the key points that relate to safety and efficacy of CPX-351. I think it is important to emphasize that it is an intensive chemotherapy drug, one that is not typically thought to be suitable for a patient with, say, a more frail status or with significant comorbidities who would not otherwise be considered a good candidate for intensive induction chemotherapy. Keep in mind that this is not a low-intensity type of drug. It is a drug that has the ability to enact a good response but is intended for patients that can tolerate more intensive therapy.

I would like to point out one key aspect of CPX-351 that distinguishes it somewhat from standard therapy from a safety standpoint, and that relates to myelosuppression. What we have observed across the board with CPX-351 is that it induces a delay in normal neutrophil and platelet recovery by about 7 to 10 days compared with traditional 7+3 chemotherapy. This is not really a surprising aspect of the drug given its pharmacokinetic profile and prolonged plasma exposure; but nonetheless, it is important to keep this in mind when treating a patient, that you may be dealing with more prolonged cytopenias. This in no way reflects decreased efficacy, it is just a safety concern to take into consideration when treating these patients, and making sure that they have appropriate transfusion support available for an extended period of time.

Now that CPX-351 has been approved for secondary and high-risk AML this past year, I think it is important for physicians and providers in the clinical and academic community to also be aware of other types of trials and studies that are relating to this agent. I think at this particular meeting here at ASH, you will be hearing a lot more about expanded safety analysis. You will be hearing about the efficacy of CPX-351 in less-fit patients – patients who would not be traditionally considered candidates for intensive therapy – and how CPX-351 at a reduced dose may be used in this patient population. There are data to describe outcomes amongst those patients. As I mentioned, we will be hearing a lot in the near future about certain combinations of CPX-351 with other targeted types of therapies that are based upon rationally designed clinical trials to take advantage of non-overlapping mechanisms and non-overlapping toxicities.

We are talking today about therapy-related AML and how it relates to de novo AML, and how it may impact prognosis and treatment decisions.

The common theme of therapy-related AML is that it is a very complex and diverse disease process that is not entirely understood. We define therapy-related AML as AML that arises following prior exposure to cytotoxic chemotherapy, generally speaking, for other cancers.

Therapy-related AML can arise at various timepoints following previous cytotoxic chemotherapy. In some instances, it can occur two to three years following chemotherapy. This often occurs in the setting of prior treatment with a topoisomerase II inhibitor as is often seen in patients with, for example, breast cancer. These types of therapy-related AML are often associated with translocations involving the MLL gene. These types of leukemia are oftentimes responsive to initial induction chemotherapy but are associated with a very poor long-term prognosis.

Then you also have a type of therapy-related AML that is associated with prior alkylating agent exposure. These types of therapy-related AML are often associated with the presence of karyotypic abnormalities such as deletion 5, deletion 7, or a complex karyotype (frequently p53 mutations); these therapy-related AMLs tend to occur after a longer period of latency, often 5 to 10 years following the prior chemotherapy. You can see that there is some diversity in therapy-related AML – both in terms of the clinical presentation and the molecular features – but overall, therapy-related AML is a disease associated with a very poor prognosis and one in which we really struggle every day to properly and appropriately treat, because the treatment options are so limited.

There is also emerging evidence that therapy-related AML may relate to preexisting clones, if you will, that predated even the initial administration of the chemotherapy for another cancer. This has been demonstrated in the setting of p53 mutations which could be unmasked and allowed to propagate in a favorable environment after chemotherapy; this is something that we see not infrequently in the setting of therapy-related AML that is associated with very poor outcomes. The presence of preexisting clonal hematopoietic abnormalities such as p53 and others is an emerging area and one that we need to focus on in terms of trying to identify such patients ahead of time, and possibly employing preventive strategies to reduce the risk of subsequent development of therapy-related AML down the road.

But once it develops, we have to think about how to treat this disease. To date, the therapeutic options are very limited. We typically think about utilizing hypomethylating agent therapy for these patients. In some circumstances, for younger fit patients, intensive induction chemotherapy may be an option. All of these types of therapies should be followed by an allogeneic hematopoietic cell transplant in the future as a way to potentially cure the disease, given the fact that we do not have curative options outside of the transplant arena. We do have the knowledge now that patients with therapy-related AML may benefit from the recently approved drug CPX-351, which is a liposomal formulation of cytarabine and daunorubicin.

The phase 3 trial that was recently performed demonstrated an overall survival advantage attributable to CPX-351 compared to 7+3 for patients that had therapy-related AML, so this is a new option for such patients who are fit and considered suitable for more intensive therapy and potentially allogeneic transplant down the line.

Thank you very much for viewing this activity.

Reference:

Lancet JE, Ritchie EK, Uy GL, et al. Efficacy and Safety of CPX-351 Versus 7+3 in Older Adults with Secondary Acute Myeloid Leukemia: Combined Subgroup Analysis of Phase 2 and Phase 3 Studies. *ASH 2017.* Abstract 2657.