What are the prognostic implications of TP53 mutations in AML and what key clinical trials show promise for future treatment?

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Welcome to *Managing AML*. My name is Dr. Nicholas Short, and I'm frequently asked, “What are the prognostic implications of TP53 mutations in AML, and what are the key clinical trials that show promise for future treatment?” If we're talking about in the frontline setting, certainly TP53 mutations are among the worst genomic abnormality and are associated with very poor outcomes. When we treat patients with hypomethylating agent plus venetoclax, for example older patients, we get a median survival in clinical trials of about 15 months, however, when patients have TP53 mutations, the median survival is significantly lower at only about 6 months.

In fact, there are a number of analyses that show that actually the addition of venetoclax may not even improve outcomes for patients with TP53 mutations and they may do similarly well with hypomethylating agents alone. We've also seen that in the variant allele frequency (VAF), so in other words, the burden of TP53 mutation, has important prognostic implications. Low TP53 VAF, typically defined as less than 20%, sometimes less than 40%, are more likely to be associated with a normal karyotype or certainly the absence of a complex karyotype. Those lower TP53 VAFs in the presence of a diploid or normal karyotype, those patients can still have reasonably good outcomes when treated with standard therapies, either intensive chemotherapy or potentially hypomethylating agent plus venetoclax, and then they're transitioned to a stem cell transplant.

In contrast, those patients who have high VAF typically, again over 20%, or certainly over 40%, and which is almost always present in the context of a complex karyotype, those patients have extremely poor outcomes. Again, the median survival for those patients is somewhere in the order of 6 months, regardless of what the therapy used is. It's very important that these patients are referred for clinical trials whenever possible. I would say the most exciting drug that we have now that's in clinical trial development for patients with TP53-mutated AML is magrolimab. Magrolimab is an anti-CD47 antibody, but is essentially a checkpoint inhibitor, like we might think of in solid tumors, but it's a checkpoint inhibitor for macrophages. It basically stimulates macrophages to kill/ingest the malignant AML cells. We've seen in clinical trials that the outcomes for patients with TP53-mutated AML who are treated with azacitidine plus magrolimab, the median survival reported at the most recent ASH meeting in 2020 was a little over 12 months. As I mentioned, historically what we see now with hypomethylating agent plus venetoclax is only about 6 months. Certainly this seems to be a very promising therapy and one that's being actively investigated in both the frontline and relapsed/refractory setting.

Now it's worth mentioning also another drug, which is APR-246. This is a drug that the mechanism of action is not completely understood, but it's thought to convert mutant P53 proteins into a more wild-type confirmation, although again the mechanism of action is not entirely understood at this time. There were some initial data suggesting promise for this drug, but currently, there was, unfortunately, a negative study shown in MDS, so there is a hold on a lot of clinical trials for this drug. That said, there are still other ongoing studies of APR 246. I think that there still could be some utility of this drug going forward if we see some promising results in other contexts. Thank you very much for viewing this activity.