ManagingAML

Chapter 3: Improving Efficacy of Mutation-specific Therapeutic Options in AML: Emerging Data and Novel Agents

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The Pan-FLT3 Inhibitor Crenolanib is Effective Against Multiple FLT3 Mutations (P552) – Richard M. Stone, MD

My name is Dr. Richard Stone, and I am a Professor of Medicine at Harvard Medical School and the Director of the Adult Acute Leukemia Program at the Dana Farber Cancer Institute in Boston, Massachusetts. Today, I will be reviewing two abstracts presented in the area of acute myeloid leukemia. The first study I will be reviewing is the data studying variant FLT3 mutations and whether they can be eradicated by cytarabine, anthracycline, and the type 2 FLT3 inhibitor crenolanib induction in adult patients with newly diagnosed FLT3, both ITD and TKD mutant AML. The background of the study is that we are seeking new therapies for patients with mutant FLT3 AML. FLT3 AML means there is a mutation in the FLT3 allele leading to an activated kinase called the FLT3 kinase, which is a transmembrane kinase. Mutations that cause activation come in one of two flavors. More common is the internal tandem duplication mutation, which is a repeat of between 3 and more than 100 amino acids in the juxtamembrane region, and the other somewhat less common flavor is the point mutation in the tyrosine kinase domain. Now, there may be additional mutations in FLT3 which also can be activating. Some of these are point mutations in the internal tandem duplication region or the juxtamembrane region. Others are novel TKD mutations and there are even a few others. We do not know in each and every case of these so-called variant mutations whether they are activating or whether they are passenger mutations, but it is probably likely that most if not all are activating mutations, and may have relevance to the leukemia pathophysiology.

In the trial in question, we have an upfront patient population that has the mutant FLT3 abnormality, either TKD, ITD, or both. All these patients underwent next-generation sequencing, so if there were any additional mutations within FLT3 or other genes, they could be discerned. This particular abstract looked at the four patients that had additional FLT3 mutations beyond those that caused an internal tandem duplication, or those that caused a point mutation in the known D835 residue in the tyrosine kinase domain. Not all FLT3 inhibitors are the same: some only hit the ITD mutation, like quizartinib and sorafenib; others hit both the ITD and TKD mutations, like midostaurin, gilteritinib, and crenolanib. So, the question was, could crenolanib "take care of" those mutations that are outside those two regions or different than those two regions? In this relatively small upfront patient trial of chemotherapy plus crenolanib in mutant FLT3 patients, four patients were found to have a so-called variant FLT3 mutation. The good news was that in each of the four cases, the combination of induction chemotherapy plus crenolanib led to remission. It was good to see that, it implies that crenolanib might have activity across a very wide spectrum of FLT3 mutations. This is important because quizartinib, for

example, does not hit the TKD mutation, and some patients who relapse after receiving quizartinib come up with a TKD mutation. The key point that we should take away is that crenolanib is a pan-FLT3 inhibitor and may be able to deal with both the more common FLT3 ITD mutations, as well as the less common but well-known TKD mutations. The remaining challenges with this study are whether these mutations were relevant to the pathophysiology and whether the activity of chemo plus crenolanib in these patients was due to just inhibiting the ITD mutation, which is present in all the patients. I think we need to learn more about the relevance of other so-called variant FLT3 mutations beyond the normal, if you will, ITD and TKD mutations.

Potency of Quizartinib in Patients with Relapsed Mutant FLT3-ITD AML (S475) – Richard M. Stone, MD

The abstract that I will be discussing now is the data looking at a historical comparison using data the UK National Cancer Research Institute (NCRI) which compared that data to quizartinib as a bridge to transplant in FLT3-ITD AML patients after failure of salvage chemotherapy. The background to this study is very interesting. We know that FLT3 inhibitors have activity in relapsed mutant FLT3 patients. Probably, the most widely studied FLT3 inhibitors in this context are gilteritinib and quizartinib. Quizartinib is a very potent and specific inhibitor that deals with the FLT3-ITD mutation which is the more common of the two well-known FLT3 mutations, ITD and TKD. Quizartinib is powerful in patients with relapsed mutant FLT3-ITD AML. The question is, how powerful is it?

Indeed, right now, there is a phase 3 study in such relapsed/refractory ITD mutant FLT3 AML patients comparing quizartinib to dealer's choice chemotherapy. The primary endpoint of that study, called QuANTUM-R, is whether or not the survival in the quizartinib-treated patients will be superior to the survival in the chemotherapy-treated patients. The goal of this study in fact was to give a little bit of a preliminary guess as to what the outcome of that big phase 3 trial is going to be. They simply looked at single-agent quizartinib data from a trial that was conducted earlier in relapsed/refractory ITD mutant FLT3 patients, and basically compared that to a historical control group of patients treated in the UK, who had relapsed/refractory AML, had a FLT3 mutation but received chemotherapy, not a FLT3 inhibitor. They found 118 patients in the NCRI database who met that criteria. In other words, they were relapsed/refractory, they had a FLT3-ITD mutation, and they were getting chemotherapy. They took out the patients that did not make it 14 days after their relapse was diagnosed to eliminate the problem of early deaths in chemotherapy. They compared the outcome, both in terms of response rate and getting to transplant and overall survival, in those patients who got quizartinib to this control group of those people who got chemotherapy. Again, the remission rate was quite a bit higher in the quizartinib-treated patients, 40% versus about 10% or 5% in those who had chemotherapy. The chance of getting bridged to transplant was higher in those who got quizartinib, and the overall survival was better in those who got quizartinib compared to these 118 patients who received chemotherapy. Even when they did a landmark analysis looking at just those patients at 120 days or so who were still alive - again getting rid of the early deaths - there was still a benefit to quizartinib. This makes our belief, or our guess, or our hope that the quizartinib versus chemotherapy ongoing phase 3 trial in mutant FLT3-ITD patients who have relapsed is going to be positive in favor of quizartinib, with an overall survival endpoint as the key endpoint. Of course, the challenge here is that quizartinib is effective against ITD but not against the TKD, so

there may be patients who relapse on quizartinib with the TKD mutation. Also, you always have the problem of historical controls in this particular study, not being representative of what is going on right now. However, I think it is certainly provocative, and as I said it provides some hope that the true phase 3 ongoing trial might be positive in favor of quizartinib.

Mutational Status Correlates with Response to Pracinostat in Older AML Patients (P207) – Ehab Atallah, MD

My name is Dr. Ehab Atallah, and I am an Associate Professor of Medicine at the Medical College of Wisconsin, Division of Hematology and Oncology in Milwaukee, Wisconsin. Today, I will be reviewing the results of a study which looked at the use of pracinostat and azacitidine in elderly patients with AML and how that correlated with mutation clearance and clinical response. This was a phase 2 study looking at the combination of a histone deacetylase inhibitor and azacitidine. In that study, we enrolled 50 patients, and they were treated with this combination. These results were previously reported, and about 40% of evaluable patients achieved complete remission, and the medial overall survival was 19 months. These results were pretty good when we compared them to azacitidine by itself. In the update at this meeting, we analyzed what specific mutations correlated with response. We noted that the response rate was higher in patients with an NPM mutation or in one of the other DNA methylation pathways such as IDH and DNMT. Unfortunately, patients with a p53 mutation did worse. Based on this interesting response, a randomized trial will be conducted to compare the efficacy of pracinostat and azacitidine versus azacitidine alone in patients with AML or in older patients with AML. The study is unique mainly because of two reasons; we identified the specific subgroup of patients who could respond to this combination, and also it was noted that as time goes by and as patients got more cycles, the level of mutation in their blood actually continued to decrease. Hopefully, with this study and with other studies in AML, we will be able to identify more subgroups that could better respond to our treatments which would hopefully lead to better personalized medicine.