Key Findings in AML: An Overview

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Welcome to *Managing AML*, I am Dr. Daver. We are pleased to present highlights in acute myeloid leukemia from the 2018 ASCO Annual Meeting in Chicago. The 2018 ASCO Annual Meeting in Chicago had a lot of new updates in acute myeloid leukemia including changes to frontline therapy in elderly acute myeloid leukemia, as well as new targeted therapies that are now emerging and will hopefully be on the market in the next few months. I am going to touch on some of these new entities as well as how we are incorporating these into our clinical practice, both at my institution (MD Anderson), but also more broadly in the community and academic setting in the United States.

I think one of the major developments in acute myeloid leukemia has been an agent called venetoclax. Venetoclax is a BCL-2 inhibitor. The BCL-2 pathway is a major anti-apoptotic pathway and so by blocking BCL-2, we are promoting apoptosis, or cell death. This is the basic mechanism of action of venetoclax. Venetoclax was initially studied as a single agent in relapsed/refractory myeloid leukemia, and it actually showed a very modest response rate of 19%. This was published in *Cancer Discovery* by my colleague, Dr. Marina Konopleva, last year.[1] Then the study was changed, and we did a frontline study where we combined azacitidine or decitabine (both are standard hypomethylating agents used in frontline treatment of acute myeloid leukemia) with venetoclax. When we did the combination, we saw a tremendous synergy when the two agents were given together. The combination of azacitidine or decitabine with venetoclax is now producing overall response rates of 75%. This is three times higher than expected response rates with azacitidine or decitabine alone, where we expect response rates in the range of 15% to 25% in frontline elderly AML patients. In addition to the response rates, the median survival is very encouraging at 18 months which is again double the median survival we would get with azacitidine or decitabine alone, and the three-year survival now is 45%.[2,3]

This is a major breakthrough. For the first time, we are able to offer meaningful treatment to our elderly acute myeloid leukemia patients: the patients we see in clinic who are 65 years of age and above, not fit for standard induction chemotherapy, and often have adverse risks, cytogenetics, or molecular features. We saw that with this combination of azacitidine and venetoclax, now in almost 200 patients treated worldwide in this large phase 2 study, we have almost a 50% chance of offering them 2-1/2 to 3-year and beyond survival which is very, very important because historically we always projected the long-term survival for elderly AML at between 10% and 15%. What was more interesting from the study that was presented at the ASCO Meeting by Dr. DiNardo, one of my colleagues, was that the responses seem to be maintained across all

molecular and cytogenetic subsets. Even people who had adverse cytogenetics as well as adverse mutations (such as TP53) seem to have 60% to 70% complete responses or complete responses with insufficient count recovery, which is very, very encouraging. Now when we look at the duration of response and overall survival, we do unfortunately see that the people who have adverse cytogenetics and TP53 mutation continue to have a decrease in their median overall survival; with a median overall survival of 8 to 9 months, as opposed to 18 months for the people who do not have these adverse features. Although these data are very encouraging and getting 45% to 50% survival in the elderly unfit population at 2-1/2 to 3 years' time point is fantastic, we still have a lot of work to do. Patients with TP53 adverse cytogenetics continue to have poor survival, and we are also seeing that at 2-1/2 to 3 years, more than 50% of people are losing response or are not alive, so we now are looking at new combinations that will further improve on the azacitidine/venetoclax. These include agents such as MDM2 inhibitors, immunotherapies and monoclonal antibodies. In fact, a number of triplet combinations looking at these are now being moved into clinical trials. Based on the exciting data of azacitidine/venetoclax, the companies AbbVie and Genentech have filed with the FDA and the filing is currently under review. We hope that by the end of this year, the combination will become approved and will be a standard of care for all elderly AML patients, especially those who are not fit for intensive chemotherapy. For the community physicians in the audience, I think it is very important to keep an eye on this developing space and once this combination is approved, I strongly believe that this should be the combination that should be used in the frontline setting, no longer using single-agent azacitidine or decitabine, but using the azacitidine/venetoclax combination.

The other major changes that we have seen are the development of targeted therapies. There are two particular mutations for which targeted therapies have moved forward very rapidly, and these are the IDH1 and IDH2 mutations, and the FLT3 mutations. There are two drugs that are being evaluated in the relapsed FLT3-mutated acute myeloid leukemia space: quizartinib and gilteritinib. Both of these drugs are second-generation FLT3 inhibitors. Both of them in large phase 2 studies with more than 200 patients have shown very high activity, producing bone marrow response and remission rates of 50% or more.[4-6] This is quite striking when you think about the fact that these are single oral agents and can produce up to 50% responses in a relapsed acute myeloid leukemia patient. Both of these agents, quizartinib and gilteritinib, have been evaluated in phase 3 trials. The phase 3 trials both are completed; and in fact, at the recent EHA meeting, the quizartinib phase 3 data were updated and it was shown that the phase 3 trial was positive with an improvement in overall survival.[7] The design of this study was that we took patients who had first salvage AML and had a FLT3 ITD mutation, and then patients were randomized in a blinded fashion in this phase 3 study to receive either single-agent second-generation FLT3 inhibitor quizartinib or investigator-choice chemotherapy. The investigator-choice chemotherapy could be either low-dose cytarabine, mitoxantrone-etoposide-cytarabine (MEC), or FLAG-IDA. Basically the idea was to see if the single-agent oral FLT3 inhibitor could produce better response rates or better survival than combination high-dose chemotherapy. The quizartinib indeed did show that there was an improvement in overall survival at 28 weeks, as compared to 21 weeks with the standard chemotherapy.[7]

What was also interesting was that the response rates with quizartinib were maintained and similar to what was seen in the phase 2 study where the overall marrow remission rates were about 50% in the phase 3 study, as compared to 25% for patients who were getting the investigator-choice chemotherapy. About double the patients, 25% to 30% of the patients on the quizartinib arm, could be bridged to a stem cell transplant; whereas only 10% to 11% of patients who got the investigational chemotherapy could be bridged to stem cell transplant. This data showed that quizartinib as a single agent in relapsed FLT3 ITD AML was a very good choice. It showed better response rates as well as improved survival compared to high-dose chemotherapy, and more patients could be bridged to transplant, which eventually is the goal in all FLT3-mutated AML patients. Based on this, the company has applied to the FDA and we expect that quizartinib will be approved and should be a standard of care in relapsed FLT3 ITD mutated patients, hopefully by the end of this year or early next year.

The other agent in this space is gilteritinib, which again is a second-generation FLT3 inhibitor, also very potent. It seems to have almost exactly the same marrow remission rates as a single agent to quizartinib of about 50%. One of the plus points with gilteritinib is that it covers both the FLT3 ITD which is the more common FLT3 mutation, but also the FLT3 D8-35 which is less common but can be a mechanism of resistance in about 25% to 30% of patients who become resistant to FLT3 inhibitors. The phase 3 study of gilteritinib versus investigator choice was almost exactly the same design as the previous quizartinib study has been completed. We do not have the topline results released yet, but we do know that the company has filed with the FDA, so we assume there must be some positive data. I think both quizartinib and gilteritinib will become available for salvage FLT3 ITD-mutated patients in the next six months. This is going to be a very good situation where we are going to have not one, but two very active second-generation FLT3 inhibitors whereas compared to in the past, we had no drugs in this space. It is going to be very critical now to start figuring out how to sequence these agents and how to build combinations with these agents, because although the marrow remission rates are up to 50%, we do know that the duration of response is unfortunately short with both quizartinib[7] and gilteritinib,[6] lasting anywhere between 14 and 20 weeks. If we can get a patient to stem cell transplant in that duration if he/she is a healthy young patient and has a good donor and financial clearance, then this is very meaningful. On the other hand, if we cannot get the patient to stem cell transplant quickly, then the duration of response of 14 to 20 weeks is clinically not as meaningful. We need to start building combinations, and a number of trials looking at combinations of azacitidine or decitabine with quizartinib or gilteritinib; chemotherapy with quizartinib or gilteritinib; as well as new agents such as venetoclax and MDM2 inhibitors with quizartinib and gilteritinib are now moving forward. Based on a lot of preclinical data, we think that these may further improve the outcomes. For the community doctors at this time, I think the key is going to be to keep an eye on the approvals for quizartinib and gilteritinib; and most importantly to check FLT3 ITD. Both at diagnosis because last year the FLT3 inhibitor midostaurin was approved to be used in combination with induction chemotherapy for newly diagnosed AML; but now more importantly I think we also need to start checking for FLT3, both ITD and D8-35, at relapse because we do know that there are some patients who may have the FLT3 ITD or D8-35 at diagnosis, but they may lose it at relapse. Vice

versa, there may be some patients who do not have a FLT3 ITD or D8-35 at diagnosis, and they may acquire it at relapse and then become eligible to receive either quizartinib or gilteritinib, which will be much better choices than giving them high-dose chemotherapy such as FLAG-IDA or MEC. This should now be considered as a standard to check FLT3 mutational testing on the bone marrow at diagnosis and at each relapse, because now this is actionable with standard agents becoming available very soon.

The next group of targeted therapies that was not discussed much at ASCO but I think is of importance for the community physicians, and has been discussed at EHA which is another meeting that happens soon after ASCO, is the IDH inhibitors. I will not go into much detail, but briefly we do have drugs now that like the FLT3 can target patients who have an IDH1 or IDH2 mutation. This makes up about 15% to 20% of acute myeloid leukemia; it is a little bit less common than FLT3 which is seen in about 35% of all acute myeloid leukemia patients, but it is an important target, and both the IDH1 inhibitor ivosidenib as well as the IDH2 inhibitor enasidenib are now available.[8,9] The IDH1 inhibitor should be available very soon on the commercial market, so we are routinely checking all our patients at relapse especially for IDH mutations.* If they happen to have either an IDH2 mutation or an IDH1 mutation, we would prefer to give them treatment with an IDH inhibitor. These have shown response rates of about 35% to 40%, so slightly lower than the FLT3 inhibitors quizartinib and gilteritinib, but are very, very safe agents. The very well-tolerated oral pills can be given at home, and a number of these responses are in fact quite durable, so I think that if I do have an IDH-mutated relapsed patient, my preference would be to go for an IDH1 or IDH2 inhibitor, rather than standard chemotherapy.

Those are the targeted agents that are now available and should be considered, but now we are going to move a little bit away and talk a little bit about the immunotherapies, which are a new group of therapies, just like in solid tumors and lymphomas, becoming more and more important in the therapy of acute myeloid leukemia. When we talk about immunotherapies, there are two major immunotherapy approaches we need to think about. One of these are called antibody drug conjugates. These are antibodies that are targeted towards leukemia-specific antigens, and in AML, those leukemia-specific antigens are usually CD33, CD123, CLL1 and TIM3. Usually they are bound to a toxic payload, either a bacterial or chemical toxin; and the idea is to direct this toxic payload into the leukemia mature blast in a preferential manner resulting in death of the leukemia cells. There is one antibody drug conjugate that is already approved in the United States. This is an agent called gemtuzumab ozogamicin. This agent is recommended to be used in combination with induction chemotherapy, especially in patients with acute myeloid leukemia who have favorable cytogenetics. This includes core-binding factor cytogenetics such as inv(16) and t(8;21) but also has shown improved survival in patients who have intermediate cytogenetics AML.

At MD Anderson, if we have a new AML, we check them to see if they have core-binding factor (inv(16) or t(8;21) cytogenetics), or if they have intermediate cytogenetics, we would offer that patient the addition of gemtuzumab to standard induction chemotherapy. We would not do that

for people who have adverse cytogenetics like del(7), del(5), del(17) or complex karyotype because the benefit was not shown by adding gemtuzumab in that group of patients. In addition to checking for FLT3, IDH1 and IDH2 that we talked about, it is also important checking the inv(16), t(8;21), and general cytogenetics of the patient because now we are really getting to first-line therapy where we could offer different targeted immunotherapies to patients based on their cytogenetic or molecular profile.

In addition to the antibody drug conjugates, there is another group of immunotherapies that depends on harnessing your own T cells. These are called T-cell activating therapies, and these include three different modalities: immune checkpoint-based therapies, bispecific antibodies, and CAR T cells. At this year's ASCO Meeting, there were data showing that if you looked at acute myeloid leukemia patients both in the bone marrow and peripheral blood, there was a well-preserved T-cell population. In fact, the T-cell population seemed to show an activated phenotype, meaning that the T cells in the bone marrow of patients with acute myeloid leukemia were actually trying to fight against the leukemia. They expressed high numbers of CD8, OX40, HLA-DR and CD69, known markers of activation.[10] This led to the hypothesis that, similar to solid tumors where we see an activated T-cell infiltrate and immune checkpoint therapies have shown activity, there may be a role for these agents in acute myeloid leukemia. One of the studies presented by Dr. Kadia, one of my colleagues, was looking at maintenance with the PD-1 inhibitor nivolumab in patients with acute myeloid leukemia who had completed their planned induction consolidation, usually with araC-based therapies, and they were not candidates for stem cell transplant. We were able to show that by adding nivolumab as a maintenance, now this is a small phase 2 study and not to be considered standard of care; but based on the data that we had in 20 patients, we saw that we were able to improve the event-free survival and overall survival, especially in patients who have adverse features such as high-risk cytogenetics, bad molecular phenotypes such as TP53, and secondary AML. In those patients, the addition of the nivolumab maintenance for a one-year period as we did in our trial improved the event-free survival to 65% and the overall survival to 80% at 1-1/2 years.[11] We will continue to follow these patients, but it does seem that there may be a role for these immune checkpoint agents. Others have previously presented and published that combinations of hypomethylating agents such as azacitidine with PD-1 inhibitors also seem to be very active, especially in relapsed AML. In early salvage patients such as salvage 1 and salvage 2, these are able to produce response rates of 30% to 40% and a median overall survival of 5.7 months or higher, which is very encouraging when we compare to historical outcomes in salvage 1 and 2 patients.[12] There are a number of studies including a randomized phase 2 study looking at nivolumab maintenance in patients who have completed induction consolidation, as well as a large phase 3 SWOG cooperative group study looking at combination of frontline therapy of azacitidine/nivolumab versus azacitidine in newly diagnosed elderly AML not fit for intensive chemo. In addition to this, there are about 25 to 30 smaller ongoing studies looking at different immune checkpoint-based therapies, as well as double immune checkpoints such as PD-1/CTLA-4 inhibitors in both relapsed and frontline acute myeloid leukemia.

As you can see, there are a lot of developments. There were four drugs approved last year for acute myeloid leukemia. These included the FLT3 inhibitor midostaurin, IDH2 inhibitor enasidenib, as well as gemtuzumab which is a CD33 antibody drug conjugate, and CPX-351 (Vyxeos) which is a fixed-dose formulation of cytarabine and idarubicin (liposome). Now this year already, we are looking at three to four potential drugs that may become available by the end of this year or early 2019. These include the two FLT3 inhibitors (quizartinib and gilteritinib), venetoclax in combination with azacitidine for frontline elderly acute myeloid leukemia, and the IDH1 inhibitor ivosidenib which is also being reviewed by the FDA.* In a span of two years, we are going to have potentially eight new drugs and this is a major breakthrough in development for acute myeloid leukemia. I would also encourage you to look at the other abstracts that have been covered in more detail by my colleagues from ASCO 2018 and a number of these covered topics that I alluded to such as the FLT3 inhibitors, venetoclax, and immune checkpoint-based therapy have more in-depth discussion of specific abstracts.

I thank you very much for listening, and I wish you a good day.

**On July 20, 2018 the FDA granted approval to ivosidenib for the treatment of adult patients with relapsed or refractory AML with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved companion diagnostic.*

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