ManagingAML

New Advances in AML Panel Discussion

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Dr. Daver: Hello and thank you for joining us. I am Dr. Naval Daver, Associate Professor at the MD Anderson Cancer Center in Houston, Texas, and I am pleased to be joined today by my two colleagues Dr. Jessica Altman, who is an Associate Professor at the Northwestern University Feinberg School of Medicine, and Dr. Alexander (Sasha) Perl, who is an Associate Professor at the Abramson Cancer Center at the University of Pennsylvania. Together we will do our best to provide you with the latest evidence in the treatment and management of AML as we explore the continuing evolving landscape and what this means for you and your patients. These are our disclosures.

Sasha, one question I was going to ask you from a practical perspective, when you get a newly-diagnosed younger AML, what molecular mutations are you testing and waiting for and what are the timelines that those are taking in your center?

Dr. Perl: We are looking at patients' core binding factor status first as we are assessing them for whether they are fit or unfit for intensive chemotherapy, that is kind of the initial decision tree that we will use. That will largely determine whether we use gemtuzumab added to frontline intensive chemotherapy, so 7+3 plus gemtuzumab versus a 7+3 with or without a FLT3 inhibitor if we are going to treat them intensively. If they are a candidate for CPX-351, we also want to look at that, so I must say we are typically using that drug in older patients because that is where we have seen prospective data that show a survival benefit. That has not been proven in younger patients, and now with the data showing that venetoclax and the hypomethylating agent, from what is available looks at least as good as azacitidine alone, and often we are trying to avoid inpatient hospitalization plus some feasibility data that were presented as shown in

transplants after Ven/Aza, we are increasingly using that as a strategy for our therapy-related patients or for those who have MDS-related AML. We are still taking patients to CPX inductions, but I'd say we are generally using it less in the era of coronavirus.
We send FLT3 testing of course, but it often is not back before we start induction chemotherapy and it comes back within a few days and we add the FLT3 inhibitor thereafter. There is also a randomized study of which FLT3 inhibitor to add that we have open our center, midostaurin versus gilteritinib, but I certainly recognize that many centers have had to completely suspend clinical trials and that has made it doubly hard to both answer these important questions and also offer best therapy to patients just because of all the of logistic hurdles of doing clinical research in coronavirus pandemic.

Dr. Daver: Alright, thanks a lot, Sasha. So, Jessica, turning over to you I was going to ask, we are all using HMA-venetoclax extensively and at MD Anderson we are using it a lot for all our older patients, is there any particular group of older patients who may not be good candidates for intensive chemo but molecularly you are not yet convinced with HMA-venetoclax or you may consider other treatments?

Dr. Altman: Thanks, Naval. I think the question that you are asking is, who is the patient that I would not be giving HMA-venetoclax to? Is there a specific molecular subtype? Before I address that I think the real kind of crux question is, in today's setting with COVID-19, who is the patient who is receiving CPX? Who is the type of patient who we think is appropriate to have an intensive induction chemotherapy with CPX and not receive HMA-venetoclax? And I think it is hard, especially in the setting of COVID-19, to find the right patient who is receiving that type of therapy. We now have increasing data that those with P53 mutations do not respond well to CPX-351. We also unfortunately have data that those with P53 mutations do not have as great of a response to HMA-venetoclax, and so this really gets kind of at your question. Those are patient populations that there is a critical need for clinical trials, as challenging as clinical trials are in this setting, it's those trials that we have kept open and are still enrolling at our institution. For instance, we have a clinical trial with Aza-venetoclax and APR-246, the P53 reactivator, and there are similar trials ongoing of CD47 compound magrolimab with HMAs. So I think that is a patient population that we really need to get our handle on, especially in the context of clinical trials today.

Dr. Daver: Yeah, no I totally agree, we are facing the same issue with the TP53, especially and I will dare say there will be data coming from our group and we did a large analysis, there is actually no benefit of the HMA/Ven versus HMAs alone, so we thought there may be some but with the longer follow-up and larger numbers they are all coming at six to eight months survival pretty overlapping curves.

What about FLT3 in older AML? Let's say you have a 70-year-old with FLT3 mutation, somebody you don't want to give induction. Would you go HMA/FLT3, HMA/Ven, or triplet, what is your thought?

Dr. Altman: This is an area of major interest to the three of us and I know many others out there as well. There is data of the doublet combination of HMA and venetoclax, and that is an appropriate option for patients, and it is a standard of care option for patients with FLT3 mutated AML who are not candidates for intensive chemotherapy. The problem with the applicability of some of that data is that trial that led to the approval required white blood cell count, I believe, less than about 25,000. And as we know, many patients with FLT3 mutated AML frequently have a high white blood cell count, and so many of the typical FLT3 patients may not have been enrolled in that study or had required to receive hydroxyurea to bring down their white blood cell count, and so that data may not be applicable to those patients. There is an ongoing study, mostly being conducted internationally, looking at azacitidine versus azacitidine and gilteritinib, and there is a little bit of data that has been presented that gilteritinib and azacitidine is not only safe but appears to have a promising response rate, but there has been very few patients that have been reported on. There is also data in the relapsed setting from your group, Naval, looking at azacitidine and sorafenib, and so we have bits of data that are coming together. Those regimens are not yet standard. There are safety data and we think promising data that we will talk about in a moment in the relapsed patient population combining venetoclax and gilteritinib. I know there is an ongoing study at your center and there are trials of interest at other centers as well looking at triplet therapy. The combination of azacitidine, venetoclax, and FLT3 inhibitors, whether that be gilteritinib or other agents.

Dr. Daver: Yes, that's another area where we feel if you look at some of the subset analysis presented at ASH, the FLT3 response rates are good, 65% to 70%, but the durability is much shorter. Andrew Wei and Courtney DiNardo published in *Blood* recently the same thing, that these are the patients who are relapsing. So personally, even if we did not have a trial, we are kind of going more for FLT3 combo, HMA/FLT3 or potentially triplet, and hopefully some of the data you mentioned with the gilteritinib/HMA or others will mature and maybe even the triplets, although myelosuppression is an issue, but yes, I think those two subsets HMA/Ven can be improved on, but otherwise we are finding very good activity in other groups.

So Jessica, you mentioned that for TP53 you are also looking at some of these new agents. Do you feel that these will have a role in AML as well, or do you think the data is more compelling robust in MDS?

Dr. Altman: So, the vast majority of the data that exists now with the APRs and MDS patient population and low burden AML, though we are participating, and very happily participating in an AML study, the one that you mentioned, the triplet combination and there are a couple of other arms on it as well, and I think we need to push for vigorously with adjustments and treatment for P53-mutated AML.

Dr. Daver: And, Sasha, what is approach at UPenn for TP53 AML or MDS, is there particular trials or interest?

Dr. Perl: I think that the agents you mentioned are the primary things that we want to be offering patients, so yes, staying away from cytotoxic agents I think is what we like to do in this setting because we think that they have very limited efficacy, even transplant has really limited efficacy but I think it is the only long-term solution for patients who have this type of leukemia and/or MDS. So yes, any trial option that looks at novel agents is what we are going to want to recommend and the really promising agents are the ones that you have mentioned previously. We do have the APR-246 study open. At our center, we have the MDS study open. We don't have the AML study open and that is something we have tried to encourage participation on.

Dr. Daver: Yes, I mean I think you made an important point though which is the community may not yet have penetrated is that I think all of us really agree that cytotoxic chemotherapy is not the way to go for these TP53. We have been murmuring about it in our groups for a while but I think with the emerging data, and we are putting together a large dataset and I know a couple of other groups are, it really does not seem to add at all, so even for young patients, 40, 45, 50, for TP53 we are just going for HMA-based combos and I think in the community those may be the really best patients to send for these trials rather than giving them 3+7 or FLAG-IDA, which probably is not really helping them at all.

Dr. Perl: So the one thing I would just say is just to follow up on that though is that there are patients who will have a P53 mutation without a complex karyotype and they seem to behave a little bit differently. They are potentially a little bit more chemotherapy sensitive, so I would not say that it's one-size-fits all here in terms of chemotherapy being a bad option. But you are right. I think overall these patients generally have a dismal outcome and as much as I can there are people who do better, it's not like they are in that group that's like core-binding factor where they do a lot, lot better. They are a little bit better but I would not in any way say that that's favorable.

Dr. Daver: No, I think you're really right and I think some of these data will be published that it's the variant allele frequency as well as presence of 17 deletion, there may be subsets that

have low variant allele frequency and non-complex that could benefit but I think really would be good ones for trial-based analysis. Now what about CAR-T cells, Sasha? UPenn has been doing a lot of the CARs for ALL, anything in the horizon for AML?

Dr. Perl: Sure. A lot of places are trying to get the same kind of efficacy in AML that's been seen in ALL, but there's also a lot of challenges in AML which you are obviously familiar with being so experienced in the immunotherapy world. The big challenge in terms of CAR-T therapy in AML is that there's not an epitope on a myeloblast that is analogous to CD19 or even CD22 where you can say it is specific for a leukemic population or even a myeloid population where you could eliminate it and not have the issues of substantial myelosuppression that could be long-lived. We can induce therapeutic B-cell aplasia in lymphoid malignancies without a big long-term complication rate because we can add back antibodies with IVIG. That is not something that we can say that we can live with if we ablate the myeloid compartment in the bone marrow, so you want a CAR-T therapy that is efficacious enough so that it eliminates leukemia but not so efficacious that it completely ablates hematopoiesis unless you are using it as a bridge to transplant, and so we are kind of interested in both of those questions. One is, can we define a therapeutic index for CAR-T therapy? And there are many different epitopes we can design CAR-Ts against. We currently just finished a study looking at CD-123 and we are not alone in that regard. A number of centers have looked at CAR-Ts against CD-123, but there are other reasons to look at other myeloid antigens and you have mentioned some of these already, whether it's CD-33, whether it's even CD-47. There are a number of different potential epitopes to go after, but the big challenge is how do you give this therapy both to induce a response and then not cause so much myelosuppression that you are left without a functioning bone marrow? We have basically designed a CD-123 CAR that initially we did animal studies and found that we are very good at ablating the bone marrow entirely in the mice, and so therefore we first did RNA-based CARs which were not efficacious enough, and then more recently lengthy viral CARs that did show efficacy but we've only done it in patients who have a transplant option immediately afterwards and we have bridged a number of these patients to transplant, sometimes out of necessity because it does really get rid of the hematopoiesis quite efficiently. So, we'll see, those data are collected. They are not yet presented. There is not a magic bullet, I would say in terms of low-hanging fruit for CAR-T therapy in AML, but that does not mean that we could develop a strategy that will take it forward and I think there are a lot of smart people in the field trying to solve this problem right now, and hopefully we will have updates sooner at major meetings.