AMLGlobalPortal

General AML

Immunotherapy approaches in acute myeloid leukemia– interview with Dr. Naval Daver

 **Naval Daver**  **Cynthia Umukoro** | Sep 20, 2018

At the 6th Annual Meeting of the Society of Hematologic Oncology, Naval G. Daver, MD, Assistant Professor, Department of Leukemia, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center (MDACC), gave a talk on "Immunotherapy in AML: Anything there."

In an interview with the AML Global Portal, Naval Daver, discussed this topic specifically focusing on the prospects and future of immunotherapeutic approaches in acute myeloid leukemia (AML). Read the full transcribed interview below (AGP: AML Global Portal and ND: Naval Daver).

AGP: What are the prospects for immunotherapy in AML?

ND: There are many different types of approaches that can be used for immunotherapies. There are four major ones in acute myeloid leukemia, including monoclonal antibodies, these are usually conjugated to some form of toxin either bacterial or chemical. There are also bi-specific antibodies, which have two receptors, one that links to CD3 on the surface of T-cells and one that links to a specific antigen on the surface of leukemia cells. This results in T-cell activation, which in turns kill the leukemic cells. One of this kind of antibody, blinatumomab, has already been approved for acute lymphoblastic leukemia (ALL) and a number of bi-specific antibodies are being evaluated in acute myeloid leukemia (AML). The third approach is immune check-point antibodies, these usually target major inhibitory checkpoints such as PD-1, PD-L1, CTLA-4 and now there is a growing list of nearly 15 immune checkpoints that are clinically relevant. These are focused on reactivating or stimulating T-cells to do their function in killing leukemia cells. A number of trials are ongoing with immune-checkpoint inhibitors. The fourth one, which recently became very popular, are CAR T-cells as well as the emerging CAR NK cells. They are a very highly potent and purified forms of immunotherapy, where instead of using immune checkpoints or bi-specifics to internally manipulate T-cell activation to fight against tumor, T-cells are extracted from the blood or bone marrow and are expanded and activated externally, which is then given as an infusion of activated expanded purified T-cells and these will then fight against the tumor.

Immunotherapy is already there in leukemia in many different ways. We already have an approval for CAR T-cell and blinatumomab therapy in ALL. In AML, gemtuzumab ozogamicin (Mylotarg®) has been approved. There is a lot of already existing clinical data, approved agents and a number of new agents that we would look forward to in the next 2–3 years for immunotherapy in AML.

AGP: Current on-going studies of immunotherapies in AML

ND: Specifically, for AML, the three major areas for immunotherapy of interest at this time include antibodies-based therapies, such as gemtuzumab ozogamicin, which is an antibody-drug conjugate with a bacterial toxin called calicheamicin that is targeted at CD33, which is a very common antigen expressed in 95–100% of the AML matured blast. Gemtuzumab ozogamicin was initially evaluated in phase II studies in relapsed AML in the United States and was approved in the early 2000s. However, in a subsequent confirmatory study, there were concerns for increased liver toxicity

VOD amongst patients and thus the drug was taken off the US market in 2010. In parallel, in Europe, there have been five large phase III studies, all of these studies show that the addition of gemtuzumab ozogamicin at a lower dose of 3 mg/m^2 to standard induction therapy improved both the event-free survival and overall survival in patients who had favorable cytogenetics which includes patients with inv(16) and t(8,21). Improved survival was also seen in patients who had intermediate or diploid cytogenetics. However, these studies did not show improvement in survival amongst patients who have adverse cytogenetics. Based on these studies, gemtuzumab ozogamicin has been reapproved in 2017 in the United States to be used in frontline therapy in combination with standard induction therapy. It has also been approved to be used as a single agent for relapsed AML. This is the only approved immunotherapy in AML.

There have been recent developments in bi-specific antibodies in clinical trials. One of these is a bi-specific CD123/CD3 DART molecule, flotetuzumab. Findings from a phase I/Ib study of flotetuzumab was presented at the 2017 Annual American Society of Hematology Meeting. Data from this study showed that at the lower doses, there was not much activity for flotetuzumab. However, at the anticipated recommended phase 2 dose and above, there was single-agent response rates of about 35–40% in relapsed/refractory AML with flotetuzumab. It was encouraging to see upwards of 30% response rates with a single-agent in relapsed AML, which is not something that we note frequently seen. Even with some of the most active agents in AML such as gemtuzumab ozogamicin or IDH inhibitors or like venetoclax, single-agent therapy gave response rates were 30% or less. Flotetuzumab is currently in the phase II stage, where there would be 80–100 more patients enrolled at recommended phase 2 dose and it will be interesting to see if the single-agent response rate of above 30% are maintained. If so, this would be very promising and might be considered for approval potentially.

There are two other bi-specific antibodies that are in early development for AML, AMG330 (CD3/CD33 bi-specific antibody) and XmAb (CD3/CD123 bi-specific antibody), and some of the clinical data from these studies would be presented at the 2018 Annual American Society of Hematology Meeting.

The third major group, in which some of the group at the MDACC have been doing a lot of research on, is the immune checkpoint-based treatment, specifically PD-1 antibodies such as nivolumab and CTLA-4 antibody such as ipilimumab. In relapsed AML, the combination of azacytidine and nivolumab, PD-1 inhibitor, was able to give about a 33–35% overall response rate which includes CR, CRi and PR. Specifically amongst early salvage AML patients, particularly, salvage 1, treated with nivolumab and azacytidine, a median overall survival of almost 11 months was observed. This is almost double of the expected median overall survival that you would see with azacytidine alone in similar salvage 1 relapse/refractory AML patients. This is encouraging and it is something that some of the larger companies are looking at potentially developing as a registration approach, looking at targeting first or second salvage patients enabling us to receive the maximum benefit of the addition of immune checkpoint antibody to hypomethylating therapy.

AGP: Did immune factors affect the response of patients treated with nivolumab and azacytidine?

ND: That is something that we have been investigating in great detail in collaboration with immunotherapy platforms at MDACC. Pre-therapy and on-therapy bone marrow and peripheral blood samples after cycle 1, 2, 4, and 8 were collected in about 80% of patients treated on our immune checkpoint studies and analyzed using flow cytometry and mass cytometry. It was observed that the most predictive markers for response with immune checkpoint therapies in AML were the pre-therapy bone marrow CD3 and CD8 infiltrates. If patients were selected based on their high CD3$^+$ or CD8$^+$ percentage, then we may be able to get higher response rates. In our population of patients treated with azacytidine and nivolumab, those who had CD3$^+$ numbers higher than 15%, which was found to be the optimal cut-off on logistic regression would have higher response rates of almost 58% and a significantly improved overall survival. I think the way that some of the experts are looking at these is that we can develop these therapies just as we developed targeted therapies such as *FLT3* and *IDH*, where we select people who have a particular mutation usually at good mutational burden and give them targeted agents. In the same way, if we want to get the maximum efficacy, where the benefit overcomes the risk of these agents, we

probably want to select patients who have high bone marrow CD3 and/or CD8 and we now have a cut-off based on our study that could be used as a cut-off for future prospective trials. If we do that we could expect response rates higher than 50% which could be a potential approval strategy for these drugs in upcoming larger studies.

AGP: Can you comment on the future of immunotherapy in AML?

ND: In AML, there are several treatment strategies that are currently being investigated. One of them is the novel cytotoxic and this includes drugs like Vyxeos® (CPX-351), the other is the targeted or molecular-based therapies, which include FLT3 and IDH inhibitors, venetoclax (Bcl-2 inhibitor), MDM2 inhibitors, some of them have been approved or close to approval. Then we have the big group of immunotherapies, which include the antibody-drug conjugates, immune checkpoints, bi-specifics. Cytotoxic and molecular therapies started development much earlier about 15–20 years ago and immunotherapies are the newer kids on the block and they have been in development, especially the bi-specifics and immune checkpoints, for only the last 3–4 years. With immunotherapies in AML, I think what we are seeing is very similar to what was seen in solid cancers like melanoma, lung, and renal cancer, where initially, it was the molecular or targeted agents that got approval and became standard of care. However, after immune therapies started appearing on the scene, ideally in combination, a lot of them actually overtook targeted agents and have now become the backbone of treatment in many of these other tumors. I think in AML, we are going in the same direction, where gemtuzumab ozogamicin has already been incorporated in the front-line setting, specifically for patients with favorable cytogenetics but also in a lot of patients with intermediate cytogenetics. Potentially, bi-specific antibodies and immune checkpoints could also become a major player in relapsed AML. They can also play a role in frontline AML especially if biomarker-driven strategies are used such as selecting patients who have high CD3 and/or CD8 infiltrates and other biomarkers that could predict for high response rates.

The AGP thanks Dr. Naval Daver for performing this interview.
