AMLGlobalPortal

General AML

ISAL 2019 | Targets for immunotherapy in acute myeloid leukemia

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On 27 February 2019, at the Acute Leukemias XVII Biology and Treatment Strategies international symposium in Munich, Germany, Gail Roboz, a member of our global steering committee, from Weill Cornell Medicine, New York, US, presented a talk discussing the targets for immunotherapy in acute myeloid leukemia (AML).[1]

Professor Roboz began by discussing the molecular heterogeneity of AML, including the variety of targets on the cell surface, in signaling pathways, and epigenetic regulators. Due to the large array of targets identified, each with high importance, Professor Roboz highlighted that focusing on a model of one drug targeting one molecular signature to provide a cure is unlikely to be successful for all patients with AML. Moreover, the utilization of the array of immunotherapy options combined with the number of targets provides a diverse complexity of therapeutic options.[2]

CD33

At present, CD33 is the only immunotherapeutic target with an approved drug currently available. Professor Roboz noted that CD33 is overexpressed in 90% of AML blast cells, making this a promising target, however, there are challenges with anti-CD33 therapy including specificity and variable expression levels. The antibody-drug conjugate, anti-CD33 antibody, gemtuzumab ozogamicin (GO), is internalized by cells and leads to cell death via DNA double-strand breaks. GO was first approved in 2000 for elderly patients with CD33-positive AML in first relapse, and later received approval in 2017 for the treatment of patients with newly diagnosed CD33-positive AML, following a period of diminished drug development interest due to toxicity. Professor Roboz identified that a similar pattern could be occurring with other drug development programs, and therefore later approvals could be seen.[3]

The ALFA-0701 (MyloFrance3) trial (NCT00927498) highlights the progress in immunotherapy to date, as well as illustrating the challenges still present with the dosing schedule and regimens of the GO and '7+3' chemotherapeutic regimen. This trial demonstrated a novel approach to approval, utilizing the primary outcome of event-free survival.[4] Furthermore, Professor Roboz highlighted the significance of GO for patients with core-binding factor AML, in which it provided a significant survival benefit.[5]

In order to progress therapy with GO, further information is required regarding combinations with venetoclax, CPX-351, and FLT3 inhibitors. Professor Roboz concluded that CD33/CD3 bispecific antibodies provide the most therapeutic promise for patients with relapsed/refractory (R/R) AML, however, this will have a time delay in order for the therapy to be developed and implemented into the clinical setting.

CD123

The transmembrane alpha chain of the interleukin-3 receptor (IL-3Rα) is overexpressed on leukemic progenitor cells, blast cells, and leukemia stem cells (LSCs), with a role in driving proliferation. The expression of CD123 is present across a large number of cell types with varying degrees of expression levels, making this a variable target. Professor Roboz discussed

the challenges this raises when using CD123 as a target, highlighting this could be due to a number of factors including the drug construct, the technology or the target. The development of CD33 and CD123 CAR T-cell therapies in patients with R/R AML have limited clinical data at present, and therefore it is important to consider the application of the therapy in the design phase.[6]

CD45 and CD70

The tyrosine phosphatase molecule, CD45, is involved in T cell development and is expressed on AML blast cells. Professor Roboz highlighted that in the phase III SIERRA trial (NCT02665065), the radiolabeled ^{131}I-BC8 antibody targeting agent, showed that engraftment was feasible following administration in patients with active AML prior to transplant.

Professor Roboz discussed the challenges faced in integrating immunotherapy into the front-line setting for patients with AML, including the high complete remission (CR) rates needed for approval and the small patient population available for first-in-human trials. However, Professor Roboz stressed that due to this challenge, it would be unlikely for immunotherapy, a challenging to manufacture and intensive therapy, to enter the front-line setting. As most patients relapse, the removal of all sub-clones and the establishment of an MRD negative status is considered beneficial for the achievement of a cure.[7]

CD70 and CD27 are expressed on AML blast cells, AML progenitor cells, and AML blast cells. The CD70 antibody, cusatuzumab, in combination with azacitidine show high responses in targeting AML blast cells and LSCs, and the therapy was well tolerated. Professor Roboz identified that the combination of azacitidine and venetoclax could be used for future randomization in trials.

Immunotherapy in the post-remission setting

The detection of measurable residual disease (MRD) in patients with AML is classified as a negative marker for survival. The achievement of MRD negativity is a challenge for drug development due to the requirement to demonstrate MRD negativity in a patient population rather than in an individual patient. Furthermore, Professor Roboz identified that MRD CR is not at present a regulatory endpoint, and it is important to consider what you are measuring, when and over what duration. This becomes critical when establishing an MRD negative status, particularly in the post-therapy setting.

Professor Roboz discussed the challenge of recruitment to post-remission trials, as patients receiving transplants have a large array of concomitant medications. Moreover, elderly patients receive HMA therapies or are generally too frail and this presents a challenge to enroll them into immunotherapeutic studies in the post-remission setting. There have been studies in the post-remission setting however these have individually faced challenges. The BATTLE study (NCT03154827) illustrates the most promise with the combination of atezolizumab and the investigational agent, BL-8040, a CXCR4 antagonist, in elderly patients with AML, which is examining MRD. However, this trial is accruing patients at a slow rate, highlighting a major challenge of trials in the post-remission setting.

Professor Roboz optimistically concluded that there have been eight drug approvals over the past two years in AML, and this demonstrates the development rate of novel therapies which provides promise to patients and physicians in the AML setting.

References

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