ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Improving Outcomes With Checkpoint Blockade in Non-Hodgkin Lymphoma

Joshua Brody, MD
Director, Lymphoma Immunotherapy Program
Icahn School of Medicine at Mount Sinai
Hess Center for Science and Medicine
New York, New York

H&O How effective are standard treatments for non-Hodgkin lymphoma (NHL)?

JB There are effective therapies for diffuse large B-cell lymphoma (DLBCL), which is the most common aggressive NHL. DLBCL has the highest incidence among NHLs, with approximately 25,000 new cases diagnosed each year in the United States. Standard therapies can be curative for approximately 60% to 65% of patients with DLBCL. The remaining patients are in a difficult situation. When standard therapies are not effective, the disease progresses rapidly.

For low-grade lymphomas, there are highly effective therapies that induce remissions in most cases. However, nearly all of these patients will ultimately relapse. Patients can live for years or even decades, but the therapies are not curative. Approximately one-quarter of patients with low-grade lymphomas will have an especially poor outcome.

H&O How is checkpoint blockade used in patients with NHL?

JB In most types of NHL, checkpoint blockade is not highly effective and is therefore used sparingly. Checkpoint blockade can be effective in a few types of NHL, such as brain lymphoma, testicular lymphoma, and natural killer T-cell lymphoma associated with Epstein–Barr virus. However, these subtypes cumulatively account for less than 5% of cases. Many fields of research are trying to improve on the efficacy of checkpoint blockade in NHL.

> Combining checkpoint blockade and in situ vaccination eliminated the vast majority of tumors in the laboratory.

H&O Is it known why patients with NHL are resistant to checkpoint blockade?

JB It is not known. Several hypotheses are driving our research. The poor outcome in NHL violates some of the known predictors of response to checkpoint blockade in other cancers. In melanoma, lung cancer, kidney cancer, and bladder cancer, response to checkpoint inhibitors seems to improve when the tumors meet certain conditions. The first condition is for the tumor to have a reasonable amount of tumor mutational burden (TMB). Checkpoint inhibitors enter the immune system and recognize tumor antigens, allowing them to attack the tumor but not healthy cells. However, what is unique about a tumor is the mutations that transformed it from healthy tissue. There needs to be a certain number of mutations to give the immune system something to recognize. Some tumors with extraordinarily high TMB

have excellent responses to checkpoint blockade. The most extreme example is a group of cancers with high microsatellite instability (MSI). Colon cancer is the malignancy that is most likely to have patients who are MSI-high (although this subset accounts for a small percentage of cases overall). Checkpoint blockade is almost exclusively effective in MSI-high colon cancer; it is not effective in the more common MSI-stable colon cancers. Diseases such as kidney cancer and bladder cancer are associated with a moderately high TMB, and they still respond well to checkpoint inhibitors. NHL also has a moderately high TMB, and theoretically should respond to checkpoint blockade. An even more provocative point is that Hodgkin lymphoma has the highest response rate to checkpoint blockade of any cancer, but has about the same TMB as NHL.

Other correlates to response to checkpoint blockade include the amount of CD8 T cells in the tumor, and the level of programmed death ligand 1 (PD-L1) expression on the tumor cells themselves or on other cells within the tumor. The CD8 T cells are the T cells that are primarily responsible for killing cancer cells. NHLs have moderate levels of CD8 T cells and PD-L1 expression. The levels are comparable to those of some cancers in which checkpoint blockade is the standard of care.

NHL therefore violates the known rules regarding response to checkpoint blockade. New hypotheses are needed to explain why NHL does not respond well to this treatment. Our research group tested 2 hypotheses: the introduction of dendritic cells and the role of lymphodepletion. We published the results in 2019.

H&O What is the hypothesis concerning the introduction of dendritic cells?

JB In an article published in *Nature Medicine*, we explored the addition of dendritic cells. This hypothesis goes well beyond lymphoma. TMB is almost synonymous with the production of more tumor-associated antigens. TMB refers to mutations measured at the gene level, and tumor-associated antigens are produced when those genes are made into proteins. The concept is highly overlapping: the more mutations, the more antigens. The importance of antigens to checkpoint blockade was already known. A critical aspect, however, is that tumors cannot present those antigens effectively by themselves. Dendritic cells are needed to effectively present the tumor-associated antigens. The discovery of dendritic cells won half the Nobel Prize in Physiology or Medicine in 2011. Several articles published in the past 10 years showed that without antigen-presenting cells, checkpoint blockade—and every type of immunotherapy—does not work. This association was observed in animal studies and confirmed in large patient data sets. In patients, the proportion of dendritic cells in the tumor correlates well with the ability of T cells to enter the tumor. A hypothesis for why checkpoint blockade does not work is that NHLs (and some other cancers) keep dendritic cells outside of tumors. We now have access to a natural protein called Flt3L, which increases the number of dendritic cells and can bring them to the tumor. Laboratory studies showed that checkpoint blockade became highly effective when used in combination with Flt3L. Beyond the laboratory, we then brought this concept into an early-phase clinical trial. We developed a "recruit/load/activate" triple therapy known as in situ vaccination that can (1) recruit dendritic cells to the tumor (with Flt3L), (2) load the dendritic cells with tumor antigens (using low-dose radiotherapy), and (3) activate the dendritic cells (using a TLR agonist immunostimulant). Basically, we tested the hypothesis that checkpoint blockade fails because tumors prevent presentation of their own tumor antigens. In patients with advanced-stage NHL, in situ vaccination induced partial and complete remissions that lasted months or years.

> Our research evaluated whether lymphodepletion and reinfusion of T cells would improve the efficacy of checkpoint blockade in patients with NHL.

Combining checkpoint blockade and in situ vaccination eliminated the vast majority of tumors in the laboratory. This strategy is now being tested in patients with NHL, breast cancer, and head/neck cancer (NCT03789097).

H&O What is your hypothesis concerning lymphodepletion?

JB The most well-known checkpoint blockade molecules are programmed death 1 (PD-1) and cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). When these molecules are agonized, they deactivate the T cells that express them. It is therefore necessary to reactivate the immune cells. Researchers are examining the best way to do so. The common gamma chain receptors are receptors for a series of cytokines, such as interleukin 2, interleukin 7, interleukin 15, and possibly interleukin 21. These interleukins are a shared family of receptors,

and their levels are linked. They are critical to the development of T cells. It may be possible to increase the development of T cells by infusing interleukins 2, 7, and 15 into patients. However, it has been difficult to identify safe, effective doses. Administration of interleukin 2 was first tested approximately 40 years ago. Safety concerns require administration of interleukin 2 in a hospital setting.

Homeostatic activation (also known as homeostatic proliferation) can be used to reinfuse T cells into the patient. This strategy is a critical component of chimeric antigen receptor (CAR) T-cell therapy. Modified T cells are reinfused into patients who have undergone lymphodepletion. We sometimes say that lymphodepletion "makes space" for the reinfused T cells. Before lymphodepletion, T cells are in a state of homeostasis. After lymphodepletion and reinfusion, there are fewer T cells with broader access to the unchanged amounts of interleukin 2, interleukin 7, and interleukin 15. Our research evaluated whether lymphodepletion and reinfusion of T cells would improve the efficacy of checkpoint blockade in patients with NHL. We call this strategy immunotransplant. It was tested in 2 ways. First, we evaluated patients undergoing standard bone marrow transplant, without the use of checkpoint blockade. Their T cells had increased receptors for interleukins 2, 7, and 15, just from homeostatic activation. This observation was confirmed in mouse studies.

We then administered PD-1 and CTLA-4 checkpoint inhibitors to mice with advanced-stage NHL, melanoma, or lung cancer. There was a drastic effect. Alone, PD-1 and CTLA-4 checkpoint blockade did not cure any of the animals of NHL. In contrast, immunotransplant cured NHL in approximately half of the mice and led to tumor regression in the rest. Similar results were seen with melanoma and lung cancer.

These results can be viewed in 2 ways. PD-1 plus CTLA-4 blockade is a standard therapy in lung cancer, melanoma, kidney cancer, liver cancer, and other settings. In lymphoma, bone marrow transplant is a standard therapy. It may be possible to improve outcomes by adding checkpoint blockade. In lung cancer, kidney cancer, liver cancer, and melanoma, the efficacy of checkpoint blockade can be improved through homeostatic activation of T cells, which is achieved by reinfusing the cells into lymphodepleted recipients.

In summary, the immunotransplant procedure consists of the following steps. First, we administer PD-1 and CTLA-4 inhibitors. We "harvest" the checkpoint-blocked T cells, and remove the remaining T cells with gentle chemotherapy or radiotherapy. We then reinfuse the checkpoint-blocked T cells, causing them to proliferate and become many times more effective at killing cancer cells. This observation was made in human studies of transplant patients and in mouse studies.

H&O Has this strategy been tested in clinical trials?

JB We initiated a clinical trial of immunotransplant among patients with relapsed, aggressive DLBCL (NCT03305445). The trial is ongoing, but preliminary results are promising. Immunotransplant has induced long-term complete remission.

H&O Would you like to share any other observations?

MK I would like to stress the importance of enrolling patients into clinical trials. In the past 2 years, there has been a revolution in immunotherapy. Some diseases have been transformed from incurable to potentially curable. This revolution was possible because patients chose to enroll in clinical trials. In some countries in Europe, up to 80% of some patients with cancer have access to clinical trials. In the United States, this percentage ranges from 5% to 10%. One reason for this low access is the lack of communication between clinicians in academic and community settings. As a clinical trial investigator, I encourage community oncologists to contact us to learn about opportunities to enroll patients into trials. The goal is to make promising therapies available to more patients nationwide.

Disclosure

Dr Brody's laboratory and clinical research teams have received research funding from Merck, BMS, Celldex, Genentech, and Kite/Gilead.

Suggested Readings

ClinicalTrials.gov. In situ vaccine for low-grade lymphoma: combination of intratumoral Flt3L and poly-ICLC with low-dose radiotherapy. https://clinicaltrials.gov/ct2/show/NCT01976585. Identifier: NCT01976585. Accessed March 23, 2020.

ClinicalTrials.gov. Nivolumab/ipilimumab-primed immunotransplant for DLBCL. https://clinicaltrials.gov/ct2/show/NCT03305445. Identifier: NCT03305445. Accessed March 23, 2020.

ClinicalTrials.gov. Vaccination with Flt3L, radiation, and poly-ICLC. https://clinicaltrials.gov/ct2/show/NCT03789097. Identifier: NCT03789097. Accessed March 30, 2020.

Hammerich L, Marron TU, Upadhyay R, et al. Systemic clinical tumor regressions and potentiation of PD1 blockade with in situ vaccination. *Nat Med*. 2019;25(5):814-824.

Marshall N, Hutchinson K, Marron TU, et al. Antitumor T-cell homeostatic activation is uncoupled from homeostatic inhibition by checkpoint blockade. *Cancer Discov*. 2019;9(11):1520-1537.