ADVANCES IN LLM

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Cellular Immunotherapy for Non-Hodgkin Lymphoma

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H&O What types of cellular immunotherapy are being investigated in non-Hodgkin lymphoma?

CB It is important to distinguish between the types of cellular immunotherapy available for non-Hodgkin lymphoma. There are 2 broad categories: chimeric antigen receptor (CAR) T cells and antigen-specific T cells. The table lists features of both. There are challenges specific to each type of therapy. CAR T-cell therapy involves gene modification, which increases the regulatory burden and the cost. Toxicity is another important challenge, as CAR T-cell therapy has been associated with grade 3 to 5 toxicities. From 12% to 28% of patients experience life-threatening toxicities. The other challenge is the need to create a unique CAR T-cell product for each patient. Research into the development of an off-the-shelf CAR T-cell product has not yet shown wide efficacy or safety. These challenges must be overcome, especially if the applicability of CAR T-cell therapy is to be broadened.

In the field of antigen-specific T cells, the most advanced approach is the use of Epstein-Barr virus (EBV)–specific T cells for EBV-associated non-Hodgkin lymphoma, in particular, posttransplant lymphoproliferative disease (PTLD). Studies have shown safety and efficacy using an off-the-shelf, "third-party" product, which is made with the cells of random donors. Each patient is then matched to the best product for him or her. These types of therapies have a response rate ranging from approximately 60% to more than 90%. They have

Table. CAR T Cells vs Multiple Antigen-Specific T Cells

	CAR T Cells	Multiple Antigen-Specific T Cells
Manufacture	• $$$$ • Gene modification	• $$ • No gene modification • Rapid manufacture
Regulatory	• Prolonged, complex regulatory control	• Regulatory control is less rigorous
Mode of Action	• Target limited repertoire of surface antigens	• Target multiple MHC-presented antigens • Antigen-specific CD4/CD8 polyclonal T cells
Efficacy	• Potent antilymphoma action in multiple trials → licensure	• Highly effective in a small number of trials
Adverse Events	• Prolonged B-cell deficiency • Life-threatening cytokine release syndrome • Tumor escape by antigen loss/downregulation	• None or minimal • Lower risk of tumor escape with antigen loss

CAR, chimeric antigen receptor; MHC, major histocompatibility complex.

remarkably little toxicity, with a rate of severe adverse events below 2%.

The biggest challenge for antigen-specific T cells is that these products have garnered less interest from pharmaceutical companies as compared with CAR T-cell therapies. It will be necessary to broaden acceptance throughout the medical community, including the pharmaceutical community, to deliver these products to all of the patients who need them.

The key to the use of immunotherapies is to closely monitor patients for toxicities because these biologic agents amplify the immune response.

H&O How are immunotherapies administered?

CB It is generally easy to administer these immunotherapies. They are usually given as an infusion on an outpatient basis. Administration of CAR T cells usually requires preconditioning with chemotherapy, such as fludarabine and cyclophosphamide. The key to the use of immunotherapies is to closely monitor patients for toxicities because these biologic agents amplify the immune response. Immune-mediated side effects are part of the body's attempt to eradicate the tumor.

H&O Can immunotherapies be used in combination?

CB In the future, I expect that many types of non-Hodgkin lymphoma will be treated with combination immune-based therapies. Strategies include T-cell therapies in combination with antibodies, checkpoint inhibitors, or small molecules that may enhance the efficacy of the immunotherapy. Some therapies are using epigenetic modifiers that upregulate the antigens on the tumor cell surface to allow T cells to better attack the tumor. At the 2017 American Society of Hematology meeting, multiple preclinical studies evaluated combination immunotherapy approaches. New clinical trials are beginning to evaluate these combinations, such as T-cell therapies with checkpoint inhibitors. The Children's Oncology Group has started a trial (ANHL1522) evaluating the anti-CD20 monoclonal antibody rituximab (Rituxan, Genentech/Biogen) plus T-cell therapy for PTLD. These T-cell therapies might also be combined with vaccines. If the field is going to move forward to a point where chemotherapy and radiation can be avoided, then it will be necessary to use these types of immune-based approaches in combination.

H&O What questions remain regarding the use of immunotherapy?

CB There are several questions regarding when to use immunotherapies. Should they be used at diagnosis, as an adjuvant treatment to standard of care? Should they be reserved for patients who relapse after treatment with the standard of care? Should they be used as a bridge to transplant, or after transplant? My suggestion is to use these therapies early in the disease to avoid subjecting patients to multiple rounds of chemotherapy, which will increase long-term and short-term toxicities. The field is currently focused on demonstrating safety in the relapsed population, but the goal is to use these therapies much earlier in the management plan.

H&O What has your research in immunotherapy shown?

CB My focus is on EBV-associated non-Hodgkin lymphoma, in patients who have undergone a transplant (ie, the PTLD setting) and patients with EBV-positive lymphoma who develop lymphoma in the immunocompetent setting. Up to 40% of lymphomas are associated with EBV, even when the patient does not have a known immune deficiency.

My original studies aimed to generate T cells specific to the tumor-associated antigens present in patients with EBV-associated lymphomas. These studies targeted the antigens LMP1 and LMP2, which are on the surface of Hodgkin and non-Hodgkin lymphoma cells that are associated with EBV in patients who are not immunocompromised. The treatment had an impressive response, with a 2-year progression-free survival rate of approximately 50% in patients with relapsed/refractory lymphoma. We published the results of that study in the *Journal of Clinical Oncology* in 2014. In early 2018, we published a follow-up study of the patients who did not respond to treatment. We developed a way to enhance immunotherapy by rendering T cells resistant to transforming growth factor beta (TGF-β). TGF-β is secreted by most human cancers, and it has devastating effects on T-cell function and proliferation in vivo. In the follow-up study, we genetically engineered EBV-specific T cells to be resistant to TGF-β. These cells were administered to

8 patients. Among the 7 patients with active disease at the time of infusion, 5 responded to treatment. There were 2 durable complete remissions. The cells were detectable more than 7 years later, and 50% of the patients in the study were alive and disease-free at the time of the analysis. There are now studies combining EBV-specific T cells with CAR T-cell therapy. Further research will evaluate combination strategies to enhance the ability of these T cells to persist and function in vivo, overcoming the immunosuppressive tumor microenvironment.

H&O Are there any other promising areas of research?

CB We have an ongoing study of T cells that target tumor-associated antigens expressed by lymphoma and leukemia cells. This work initially focused on the autologous setting, and it began when I was at Baylor College of Medicine. At Children's National, research has continued in patients who developed relapsed disease after allogeneic transplant. Currently, response rates are similar to those seen with CAR T-cell therapy; the complete response rate was approximately 67%. The study has shown remarkably little toxicity, despite the fact that these patients are at very high risk, having relapsed after allogeneic transplant. It is an exciting time to be involved in immunotherapy in general, and cell therapy in particular. We are already treating patients differently today than we would have even 3 years ago. In the next 5 years, there will be dramatic changes in the way we treat patients with non-Hodgkin lymphoma. The field is rapidly growing and changing. Advances are occurring almost every day.

Disclosure

Dr Bollard is a member of the scientific advisory boards of NexImmune, Cellectis, and Torque.

Suggested Readings

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