ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Adoptive Cell Therapy for Ovarian Cancer

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H&O What are the shortcomings of existing therapies for ovarian cancer?

KO Standard therapy in patients with newly diagnosed ovarian cancer consists of neoadjuvant chemotherapy followed by debulking surgery and then adjuvant chemotherapy. In addition, patients whose tumors harbor *BRCA* mutations or have evidence of homologous recombination deficiency benefit from maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors. Some patients with relatively high-risk disease also appear to benefit from maintenance therapy with bevacizumab, although the evidence for this is less compelling than that for PARP inhibition.

Despite the availability of all these treatments, the 5-year overall survival rate is still less than 50%, with most patients experiencing relapse between 12 and 18 months after treatment. A major reason for this low rate is the development of resistance to chemotherapy, PARP inhibition, and antiangiogenic agents. We do not have any effective salvage therapies once resistance occurs, which explains why many patients ultimately succumb to the disease.

H&O What makes adoptive cell therapy a promising alternative?

KO Adoptive cell therapy is very promising because we are harnessing large numbers of T cells that can recognize and destroy tumor cells. Early studies by our group and others indicated that the outcomes of patients who have ovarian cancer with high numbers of tumor-infiltrating lymphocytes (TILs) are significantly better than those of patients with a low degree of infiltration.[1,2] If we dig deeper, we find that many of the T cells infiltrating ovarian tumors are in fact bystander T cells, which are irrelevant for tumor recognition. A very nice paper that was published in *Nature Medicine* a few years ago showed that the frequency of true tumor-specific T cells is about 10%.[3] One of the major advantages of adoptive cell therapy is that it allows us to increase the number of tumor-specific T cells, even if they continue to make up only a small percentage of the whole.

H&O What forms of adoptive cell therapy are being developed for use in ovarian cancer?

KO The main forms of adoptive cell therapy that are being developed for use in ovarian cancer are TIL therapy, T-cell receptor (TCR) therapy, and chimeric antigen receptor (CAR) T-cell therapy.

Regarding TIL therapy, which I discussed earlier, many of the studies using TILs in patients with ovarian cancer produced disappointing results,[4] which I suspect were caused by the high number of bystander T cells. To overcome this problem, several approaches are being used to enrich for tumor-specific T cells in TIL therapy. One approach is to enrich for tumor-specific T cells by using markers such as programmed death 1 (PD-1), 41BB, CD137, and CD103. Another approach is to enrich for neoantigen-specific T cells, although some of the trials that were initiated to test this approach were discontinued because of the laborious and expensive nature of the process. Combination approaches with immune checkpoint inhibitors are currently in clinical trials.

The main advantage of TCR T-cell therapy is its specificity; TCR T cells recognize the antigen target only in the context of the appropriate major histocompatibility complex. Conceptually, this degree of specificity also means that the potential for adverse events is lower than that associated with CAR T-cell therapy. Our group has focused to a large degree on the use of TCR T cells that target the tumor antigen New York esophageal 1 (NY-ESO-1).[5,6] Other studies have looked at the use of TCR T cells against melanoma-associated antigen 4 (MAGE-A4) in patients with ovarian cancer, with promising results.[7] Despite the encouraging results, the use of TCR T cells has 2 major limitations. The first is that the patient needs to have a certain human leukocytic antigen (HLA) type to benefit from TCR T cells, so that the number of candidates is restricted. Hundreds of patients may need to be screened to identify a few dozen who have adequate NY-ESO-1 expression as well as the appropriate HLA type. Second, the expression of tumor antigens in ovarian cancer is generally heterogeneous, so certain areas of the tumor may be positive for a tumor antigen while other areas may be negative or have very weak antigen expression. The areas of the tumor that are distinctly negative for the antigen are unlikely to respond to the T cells; some of the areas that are weakly positive initially also may not respond, so they too escape from immune attack.

The third option for adoptive cell therapy is to use CAR T cells, which have the advantage over TCR T cells of not having any HLA restrictions. CAR T-cell therapy has shown superb clinical efficacy in liquid tumors, which gives us hope that somehow we can make it work in solid tumors such as ovarian cancer. The major limitation of CAR T-cell strategies is that you need to identify a target that is expressed on the surface of the cell, whereas the target can be intracellular in TCR T-cell therapy. Not many cell surface targets in ovarian cancer have strict tissue-restricted expression (ie, are not expressed in normal tissues), so the rate of off-target effects remains high. Common adverse events with CAR T-cell therapy are cytokine release syndrome, macrophage activation syndrome, and immune effector cell–associated neurotoxicity syndrome (ICANS). Moreover, with CAR T-cell therapy, a higher tumor antigen density is required per cell than with TCR T-cell therapy to initiate a response. Nevertheless, CAR T-cell therapy offers significant promise.

The most frequently used form of CAR T-cell therapy in clinical trials right now uses the second-generation CARs that incorporate stimulatory molecules such as 41BB and CD28. Third-generation CARs are now being studied that incorporate additional costimulatory molecules, such as OX40. Also in development are fourth-generation CARs, which are designed to release payloads such as cytokines when they arrive at the tumor site. For example, these "armored" CAR T cells could be modified to secrete proinflammatory cytokines, like interleukin 12, expressing enzymes that degrade a tumor's stroma or antibody fragments that counter immune checkpoints.

Although the first trial of CAR T-cell therapy, targeting folate receptor alpha, did not produce any clinical responses, ongoing CAR T-cell trials are looking at targeting HER2, mesothelin, MUC16/CA125, and the adhesion molecule EPCAM. Also, in ongoing studies of universal (allogeneic or "off-the-shelf" CAR T-cell therapy), T cells are harvested from healthy donors rather than from the patient's own cells. This approach allows faster treatment and reduces the need for the costly manufacturing of patient-specific cells.

An approach that applies to both TCR T cells and CAR T cells is disruption of some of the immune inhibitory signals within T cells. Examples include disrupting the transforming growth factor beta (TGF-β) signaling pathway or the PD-1 signaling pathway so that the T cells are rendered insensitive to TGF-β or PD-1. Our group has conducted a trial with TCR T cells that have been rendered insensitive to TGF-β, which is a dominant mechanism of immune suppression within the ovarian tumor microenvironment (NCT02650986). The T cells contain a decoy receptor for TGF-β, so they are not inhibited when they encounter it. These types of advances in engineering are likely to enhance our ability to increase the effectiveness of CAR T-cell therapy and TCR T-cell therapy in the future.

H&O What are some of the response rates to adoptive cell therapy in ovarian cancer that are being seen in clinical trials?

KO The best responses we have seen in many of these trials are stabilization of disease. Response rates are less than 30% when either TILs or TCR T cells are used, and up to 20% with CAR T-cell therapy.

H&O What types of ongoing research are looking at each of these methods in ovarian cancer?

KO We need increasingly sophisticated genetic engineering to make adoptive cell therapy effective. Even if we select the appropriate TIL, TCR T cell, or CAR T cell, we are asking the cells to do a lot of things: travel to the tumor site, destroy the tumor, and take up residence at the tumor site. For example, what are the critical chemokine receptors that are needed to engineer the T cells further? How do we engineer the cells to overcome the multiple mechanisms of immunosuppression? Ongoing studies are investigating the best ways to accomplish all these steps.

Some of the studies that are currently ongoing

combine treatments because we may be able to identify pharmacologic or biological approaches to enhance the efficacy of CAR T cells and TCR T cells further. For example, ongoing studies are looking at the combination of adoptive cell therapy and immune checkpoint inhibition in ovarian cancer.

Our group believes that the tumor microenvironment in ovarian cancer is particularly immunosuppressive, with both cellular and metabolic elements contributing to immunosuppression. We are developing strategies to break down some of the immunosuppressive network, such as combining adaptive cell therapy with the targeting of tumor-associated macrophages and myeloid-derived suppressor cells within the tumor microenvironment. Another approach is to block regulatory T cells, which are also highly immunosuppressive. We are currently developing a clinical trial in which an oncolytic vaccinia virus (OVV) has been engineered to express molecules that can block multiple aspects of the immune suppressive network, and we are in the process of submitting an investigational new drug application to test this approach in a clinical trial. Our goal is to combine adoptive cell therapy with the engineered OVV approach.

H&O Which patients with ovarian cancer are the best candidates for adoptive cell therapy?

KO The best candidates for TCR T-cell therapy and CAR T-cell therapy are those who receive the treatment earlier rather than later, when they are in poor physical condition and may have lost the ability to manufacture high-quality T cells for us to harvest. Unfortunately, many patients come to adoptive cell therapy late in the evolution of their disease, sometimes after as many as 4 to 7 previous lines of treatment.

As for TIL therapy, the best candidates are those who have a relatively high tumor mutation burden. Such patients are likely to have a high neoantigen burden, which means that more tumor-specific T cells may be present in their tumor microenvironment.

H&O When do you expect these therapies to become available outside clinical trials for patients with ovarian cancer?

KO If you had asked me this question a couple of years ago, I would have said maybe within 5 years, but the pace of development of adoptive cell therapies outside clinical trials has slowed. This is largely because of the increasing traction of other, less expensive and less labor-intensive modalities during the past few years. The field has gravitated toward the use of antibody-drug conjugates and bispecific antibodies, which have certainly produced some clinical benefit in ovarian cancer, but we are beginning to see some failures with those approaches. As a result, I think that we will see a resurgence of interest in adoptive cell therapies, which by definition are living drugs that can persist in the body and provide long-term effectiveness.

H&O Is there anything you would like to add?

KO Unfortunately, the field of immunotherapy has not benefited patients with ovarian cancer as much as it has benefited patients with many other solid tumors. Of the multiple US Food and Drug Administration approvals of immune checkpoint blockade for most solid tumors, none are for ovarian cancer. This is not because of lack of effort. Several large clinical trials have been conducted of combination therapies that include frontline immunotherapy as adjuvant and maintenance treatments.[8,9] The results have been disappointing, and we do not have a single immune checkpoint inhibitor approved for ovarian cancer. Strategies to improve outcomes in patients with ovarian cancer are urgently needed, and adoptive cell therapy holds promise to be the approach to take maximum advantage of the ability of the immune system to recognize and destroy tumor targets.

Disclosures

Dr Odunsi is a cofounder of Tactiva Therapeutics.

References

1. Sato E, Olson SH, Ahn J, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. *Proc Natl Acad Sci USA*. 2005;102(51):18538-18543.

2. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348(3):203-213.

3. Scheper W, Kelderman S, Fanchi LF, et al. Low and variable tumor reactivity of the intratumoral TCR repertoire in human cancers. *Nat Med*. 2019;25(1):89-94.

4. Amaria R, Knisely A, Vining D, et al. Efficacy and safety of autologous tumor-infiltrating lymphocytes in recurrent or refractory ovarian cancer, colorectal cancer, and pancreatic ductal adenocarcinoma. *J Immunother Cancer*. 2024;12(2):e006822.

5. Matsuzaki J, Tsuji T, Chodon T, Ryan C, Koya RC, Odunsi K. A rare population of tumor antigen-specific CD4+CD8+ double-positive αβ T lymphocytes uniquely provide CD8-independent TCR genes for engineering therapeutic T cells. *J Immunother Cancer*. 2019;7(1):7.

6. Matsuzaki J, Tsuji T, Luescher IF, et al. Direct tumor recognition by a human CD4(+) T-cell subset potently mediates tumor growth inhibition and orchestrates anti-tumor immune responses. *Sci Rep*. 2015;5:14896.

7. Hong DS, Van Tine BA, Biswas S, et al. Autologous T cell therapy for MAGE-A4+ solid cancers in HLA-A*02+ patients: a phase 1 trial. *Nat Med*. 2023;29(1):104-114.

8. Monk BJ, Colombo N, Oza AM, et al. Chemotherapy with or without avelumab followed by avelumab maintenance versus chemotherapy alone in patients with previously untreated epithelial ovarian cancer (JAVELIN Ovarian 100): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2021;22(9):1275-1289.

9. Moore KN, Bookman M, Sehouli J, et al. Atezolizumab, bevacizumab, and chemotherapy for newly diagnosed stage III or IV ovarian cancer: placebo-controlled randomized phase III trial (IMagyn050/GOG 3015/ENGOT-OV39). *J Clin Oncol*. 2021;39(17):1842-1855.