The Bad and the Good News on Cancer Immunotherapy: Implications for Organ Transplant Recipients

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Cancer immunotherapy, especially the use of checkpoint inhibitors, is expanding and can be efficacious in organ transplant recipients with malignant neoplasia. In this review, we summarize clinical findings and evolution of several patients treated with CTL4-4 or PD-1 inhibitors reported in the literature. The CTL-4 inhibitor ipilimumab has been safely used in several liver and kidney allograft recipients. PD1-inhibitors look promising for tumor shrinking, but acute rejection is the rule, so they should be avoided in recipients of life-saving organs. Immunosuppression minimization, especially calcineurin inhibitor withdrawal is needed for adequate responses to checkpoint inhibitor treatments. The addition of sirolimus or everolimus may be helpful for mitigation rejections. The future will tell if selective boost of cancer-specific T-cell repertoire, possibly with the help of anticancer vaccines or adoptive T-cell transfer, will improve outcomes and decrease undesirable events.

Key Words: Checkpoint inhibitors, Ipilimumab, Pembrolizumab, Nivolumab, Organ transplantation, Rejection

CANCER IMMUNOTHERAPY

In recent years, we have seen many revolutionary innovations in the treatment of cancer disease. Arguably, cancer immunotherapy represents the most important innovation.[1,2] Indeed, various trials have shown that cancer immunotherapies are effective for treating patients with various difficult-to-treat cancers, many of whom had exhausted all traditional treatment options.[2] Besides greater efficacy, immunotherapies are better tolerated than standard chemotherapy and they are also not nephrotoxic. Even more importantly, their therapeutic effect may persist longer after stopping the treatment.[2] Ongoing studies are now examining whether the treatment effect is potentiated by combining different immunotherapy treatments[1-3] and combining immunotherapies with traditional treatments, such as chemotherapy or radiotherapy.[1,2,4]

Cancer immunotherapies are based on the use of T cells as the anticancer drug. T cells can be activated in 3 major ways: first, by the use of checkpoint inhibitors, which are antibodies directed against immune-regulatory checkpoint molecules expressed on T cells; second, through adoptive transfer of anticancer T cells; and last, through induction in vivo by vaccination or endogenous delivery of neoantigens subsequent to other anticancer therapies.[1] Among the 3 approaches, the use of checkpoint inhibitors is by far the one that has achieved the most impressive results in the clinical practice to date. After being originally successfully for the treatment of metastatic melanoma and lung cancer, checkpoint inhibitors are now showing to be effective in an increasing range of cancer types that are resistant to traditional treatments, such as bladder, kidney, liver, head and neck cancer, and recurrent Hodgkin lymphoma.[2,5]

CHECKPOINT INHIBITORS

Checkpoint inhibitors are biologic drugs that block the T-cell inhibitory proteins CTLA-4 (cytotoxic T-lymphocyte associated antigen 4) and PD-1 (programmed death-1). CTLA-4 is a cell-surface receptor expressed by naive T cells during priming, with homology to the T-cell activator costimulatory molecule CD28. PD-1 binds programmed death ligand 1 (PD-L1), a protein expressed by neoplastic, endothelial, and immune cells. Binding of PD-L1 to its receptors suppresses T-cell migration, proliferation, and cytotoxic activity. Therefore, CTLA-4 and PD-1 regulate distinct phases of T-cell differentiation and function, and their inhibition has synergistic effects.[1,2] In normal conditions, CTLA-4 and PD-1 serve to prevent excessive activation of T-cell responses, minimizing the risk that an overzealous activation of effector T cells in the course of the regular immune responses to common pathogens eventually lead to serious damage of healthy tissue. Therefore, in the setting of the immune response to cancer, immune checkpoint blockade can unleash the power of naturally occurring T cells by eliminating the negative signals that block T-cell function.[1]

The first immune checkpoint inhibitor to be approved by the Food Drug and Administration was ipilimumab, a CTLA-4 inhibitor. By the end of 2014, nivolumab and pembrolizumab, both PD-1 inhibitors, were also approved. Ipilimumab and nivolumab are the only checkpoint inhibitors approved in Europe at the time of this writing. The most recent checkpoint inhibitor to be introduced is atezolizumab, which blocks PD-L1 on tumor cells. Ipilimumab was the first treatment to improve survival in patients with advanced melanoma. Recent evidence suggests that PD-1 inhibitors may be even more effective than ipilimumab. In fact, patients whose tumors stopped responding to 1 type of immune checkpoint inhibitor (eg, ipilimumab) may still benefit from a different checkpoint

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Financial Disclosure: The authors report no conflicts of interest.

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1548-5595/$36.00

http://dx.doi.org/10.1053/j.ackd.2016.08.002

inhibitor (eg, nivolumab or pembrolizumab). At the present time, combination therapy of checkpoint inhibitors is the most promising strategy for patients with advanced melanoma.[5]

Overall, in patients with advanced melanoma receiving combination treatment, the chance of experiencing tumor shrinkage is greater than 50%. Thus far, combination therapies have been mainly experimental in advanced melanoma.[2] In other form of cancers, in which checkpoint inhibitors have being used only as monotherapies so far, treatment with PD-1 inhibitors is associated with tumor shrinkage in about 20%-25% of the patients.[2] Although exceptional, cases of complete disappearance of the tumor have been documented.[2]

However, the fact that only a minority of cancer patients have demonstrated tumor shrinkage cannot be regarded as a disappointing finding by any means. First of all, the likelihood of tumor shrinking may be predicted by tumor-based and systemic biomarkers, some of which have already been adopted in clinical practice. For instance, high expression of PD-1 or PD-L1 on infiltrating T cells, endothelial and cancer cells have been associated with increased response to checkpoint inhibitors.[6,7] Additional biomarkers may be measured in the future, with the aim at assessing the way the tumor microenvironment affects the immune response. Indeed, chronic inflammation, which is often linked with the presence of T helper cell-2 responses, promotes neoplastic cell survival, angiogenesis, and metastasis, whereas acute inflammation, which is linked to T helper cell-1 responses, triggers neoplastic cell destruction.[1]

It may not only be possible to anticipate those patients who will respond to treatment with checkpoint inhibitors, but in the near future, it will also be possible to manipulate the immune system to increase the likelihood of treatment response. Examples are represented by drugs that are able to modify the chronic inflammatory microenvironment (for T helper cell 2-blockade therapies) or by the treatment strategies that use cancer neoantigen to expand the pool of anticancer T cells. Indeed, even standard anticancer treatments, such as radiation therapy or chemotherapy, cause the release of neoantigens from dying neoplastic cells that are captured from dendritic cells and presented to naive T cells. Therefore, treating with checkpoint inhibitors during the course of radiation therapy or chemotherapy may increase the response to checkpoint inhibitors themselves. In this regard, even more promising is the use of exogenous cancer neoantigens to prepare vaccines, which are able in vivo to expand or generate clones of cancer-specific T cell or the ex vivo adoptive transfer of anticancer T cells.[1,2]

CLINICAL SUMMARY

- The indications for the use of checkpoint inhibitors are expanding and can be highly efficacious in transplant recipients suffering from malignant neoplasia.
- The CTLA-4 inhibitor ipilimumab has been safely used in several liver and kidney allograft recipients.
- PD1-inhibitors look promising for tumor shrinking, but acute rejection is the rule, so they should be avoided in recipients of life-saving organs.
- Immunosuppression minimization, especially calcineurin inhibitor withdrawal is needed for adequate responses to checkpoint inhibitor treatments.

Therefore, it is likely that in the future all patients with cancer will be treated with checkpoint inhibitors, either directly or after interventions targeting inflammation, after vaccination, or after adoptive T-cell transfer.[1]

CHECKPOINT INHIBITORS IN ORGAN ALLOGRAFT RECIPIENTS

Checkpoint inhibitors can be highly efficacious in "transplant recipients suffering from cancer" as they unleash T cell immune responses against cancer cells that are impaired because of the anti-rejection treatment. Unfortunately, by checkpoint inhibitors could activate alloreactive T cells leading to acute rejection and graft loss.

The few reports that have been published to date regarding the use of checkpoint inhibitors in transplant recipients are summarized in Table 1. The first 4 patients did not develop rejection. There were 2 kidney[8] and 2 liver transplant recipients[9,10] with advanced melanoma that were treated with the CTLA-4 inhibitor ipilimumab. At the time of ipilimumab treatment, the 2 liver transplant recipients were treated with low-dose prednisone plus very low-dose tacrolimus and low-dose rapamycin, respectively, whereas the 2 kidney transplant recipients were treated only with prednisone. Interestingly, the patient on tacrolimus was the only one who fell short of showing tumor shrinkage after treatment with ipilimumab. The liver transplant recipient treated with rapamycin at the time of ipilimumab treatment, not only showed tumor shrinkage but also experienced a transient increase in aspartate aminotransferase or alanine aminotransferase levels more than 200 IU/L. Unfortunately, the patient could not be investigated by liver biopsy to rule out graft rejection. The use of rapamycin is an attractive option as it has recently been shown in mice that T-box protein expressed in T cells–dependent cancer immunosurveillance by tumor-reactive CD8 T cell is profoundly inhibited by cyclosporine but not by rapamycin.[11]

At variance with the patients who received the CTLA-4 inhibitor ipilimumab, the 4 patients treated with PD-1 inhibitors eventually developed acute rejection and graft loss (Table 1). All of them were kidney transplant recipients.[12-15] Two received PD-1 inhibitor therapy (pembrolizumab and nivolumab, respectively) shortly after the CTLA-4 inhibitor ipilimumab (ie, they received combination treatment with CTLA-4 and PD-1 inhibitor). One of them also received concomitant radiation therapy, a treatment that, as outlined earlier, has the potential to boost the effect of checkpoint inhibitors.[10,14] Graft loss, which occurred days to weeks following PD-1 inhibitor