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Use of Immun Checkpoint Inhibitor Ipilimumab in Renal Transplant Patients with Advanced Cancer: Is Risk/Benefıt Ratio Dilemma?

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Abstract: End stage kidney disease is one of the most common diseases seen worldwide with high morbidity and mortality rate. Given current renal replacement therapies, the most effective method is renal transplantation compared to dialysis. Renal transplantation improves the patient's quality of life and complications related to dialysis are minimized. Long-term immunosuppressant therapy is applied to transplantation patients to ensure organ continuity by reducing the risk of acute rejection. Survival time after renal transplantation and increased use of immunosuppressive drugs increase the risk of developing metastatic tumors in these patients. It is predicted that immune checkpoint inhibitors applied to cancer patients can be used in patients with cancer development after transplantation. Ipilimumab is a cytotoxic T-lymhocyte-associated antigen 4 (CTLA-4) inhibitor developed specifically for use in metastatic melanoma patients and approved by the FDA in 2011. The effect of ipilimumab on allograft survival has been reported compared to other immune checkpoint inhibitors. Based on these data, we examined the renal case reports available in the literature to evaluate the relationship between cancer outcome and graft rejection.
Keywords: CTLA-4, ipilimumab, melanoma, PD-1, rejection, transplantation.

1. Introduction

Renal transplantation is an effective treatment method for late kidney patients. With transplantation, the patient's quality of life improves and the risk of mortality due to complications caused by dialysis is reduced. Renal transplantation is alive or cadaveric depending on the source of the donor organ. These patients use long-term immunosuppressants to reduce the risk of acute rejection, maintain the transplanted organ and increase renal function. Survival time after renal transplantation and increased use of immunosuppressive drugs increase the risk of developing metastatic tumors in these patients (1, 2). Although the effect of immune checkpoint inhibitors has been shown in more than 20 types of cancer (3) this treatment protocol has not been applied to organ transplant patients (4). However, the critical effect of CTLA-4 antibody preventing solid organ rejection (5) and maintaining allograft tolerance of PD-1/PD-L1 interaction in peripheral tissues has been reported (6, 7). Therefore, available data have suggested the idea that immune checkpoint inhibitors can be used in patients with cancer development after transplantation. Ipilimumab is a CTLA-4 inhibitor developed specifically for use in metastatic melanoma patients and approved by the FDA in 2011. It has been reported in the literature that ipilimumab use is more effective on allograft survival compared to other immune checkpoint inhibitors (8).

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Although the alternatives used for the treatment of cancers in renal transplant patients are limited, we examined the renal case reports available in the literature to evaluate the relationship between cancer outcome and graft rejection.

1.1. Renal Transplant Rejection

The definition of rejection was first described as "biocompatibility" by Alexis Carrell in the early 1900s (9). Rejection is an immunological reaction to donor antigens recognized by the recipient's immune system. Renal transplantation is an effective remedy for patients with end-stage renal disease. The first successful renal transplantation was carried out between identical twins in the United States in 1954 (9). Regression risk is one of the most important problems in long-term allograft survival despite developing surgical techniques and immunosuppressive drugs (10). Pathological changes detected in the late 1960s have been reported to be associated with acute and chronic renal allograft rejection (11, 12). Rejection pathology can be seen in 4 different components of the kidney-glomeruli, tubules, interstitium and vessels either separately or with a combination of these regions (13). In the most common rejection cases, renal allograft biopsies show morphological damage resulting in cellular or antibody-related mechanisms. This damage is classified as acute or chronic due to graft survival and rejection activity after transplantation (13).

1.2. Rejection Types

Rejection is the adaptive immune response seen through T cell and humoral immune mechanisms. It is characterized by delay and disruption in early graft function. There are 3 major rejection forms: hyperacute, acute and chronic. Biochemical changes such as fever, malaise, tenderness on graft, graft enlargement, low urine, and increased serum creatinine and decreased glomerular filtration rate are associated with acute rejection. Acute rejection usually develops in the first month after transplantation, but it can be seen later. Chronic rejection, also known as chronic allograft nephropathy, is characterized by slow decline in graft function, often associated with hypertension and proteinuria. Biopsies performed on the first day following the transplantation to patients whose previous graft functions were delayed and then repeated at regular intervals were the diagnostic procedure for rejection. However, the expansion (enlargement) of histological lesions and subjectivity in interpretation of their severity was insufficient in establishing the diagnosis of rejection. For this reason, Banff Scheme was created to standardize renal biopsy interpretations. With this scheme, the lesions were classified for the diagnosis of acute and chronic rejection, and the types of histological findings were classified and the lesions were exacerbated (14-17).

When acute and chronic rejection is evaluated from an etiopathogenic point of view, it is seen that it is mediated by T cells and antibodies (14, 16). T cell mediated rejection is the most common early rejection type with its major features such as tubulitis and vasculitis (15). In chronic active T cell-mediated rejection, inflammatory cells in fibrotic intima and elasticity are impaired (15, 16). Alloantibodies against HLA class I, II and other antigens can be caused by both acute and chronic humoral rejection (18, 19). Although acute and chronic rejection is characterized by Cd4 accumulation in peritubular capillaries, at least 3 of 4 findings must be present for diagnosis: arterial intimal fibrosis, interstitial fibrosis / tubular atrophy, duplication of the glomerular basement membrane and lamination of peritubular capillary basement membranes (20-23).

1.3. Immun Checkpoınt Inhibitors

The life of the T cell begins in the thymus, where a large TCR repertoire is created and the immature cells undergo proliferation through the combination of T cell receptor (TCR) gene segments. T cells that bind strongly to their own peptides are eliminated in the thymus to prevent autoimmunity (24). While T cells that are insufficient to bind to MHC undergo apoptosis, T cells that are poorly attached to MHC and their peptides are released into the spleen, blood and lymphatic organs as naive cells. Some T cell receptors (TCR) may have cross-reactive specificity with their antigens. To prevent autoimmunity, many immune checkpoint pathways regulate the activation of T cells throughout the immune response called peripheral tolerance (24, 25). These pathways are cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) pathway and programmed cell death protein-1 (PD-1) pathway (25). Immune checkpoint therapies targeting these pathways provide clinical advantage for patients with malignant diseases (26).

1.4. CTLA-4 Pathway

T cell activation is a complex process that requires multiple stimulating signals. A T cell receptor (TCR) that binds to MHC provides specificity for T cell activation. However, activation mostly requires the presence of co-stimulatory signals. CD28 molecules in T cells cause the signal in T cells together with B7-1 and B7-2 molecules on antigen presenting cells (APC). Adequate level of CD28: B7-1/2 binding causes proliferation in T cells, increasing survival and differentiation of T cells through the production of cytokines such as IL-2 (27). CTLA-4 is a CD28 homologue with a high binding affinity to B7 (28). However, unlike CD28, CTLA-4 connected to B7 does not generate a stimulating signal. Competition between CD28 and CTLA-4 binding to B7 determines whether T cell will undergo activation or anergia (29).

Some findings show that CTL4-A, which binds to B7, produces inhibitory signals that inactivate stimulating signals in relation to TCR: MHC and CD28: B7 binding (30). Mechanisms associated with inhibitory signals are associated with these reasons, which are seen as a result of a decrease in the ability to interact with APCs due to direct inhibition of the TCR immune synapse, CD28 or inhibition of the associated signal pathway or increased mobility of T cells (31, 32). CTLA-4 is localized in intracellular space in naive T cells at rest (33). With the stimulating signals that result in both TCR and CD28: B7 binding, an increase in the regulation of CTLA-4 is observed on the cell surface with exocytosis of vesicles containing CTLA-4 (33). Activation of T cells is prevented by negative signal that occurs by CTLA-4:B7 binding (34). Regulatory T cells (Treg) control the functions of effector T cells. For this reason, Treg cells play a key role in maintaining peripheral tolerance. Unlike effector cells, Treg cells express CTLA-4, which explains the suppressive functions of Treg cells (35). In animal models, genetic CTLA-4 deficiency in Treg cells has been reported to impair suppressive functions (35, 36). The mechanism that suggests that Tregs control effector cells is associated with a decrease in the regulation of B7 ligands on APCs, which causes decreased CD28 co-stimulation (36, 37).

1.5. PD-1 Pathway

Programmed cell death protein-1 (PD-1) is a member of the B7/CD28 family. It regulates T cell activation by binding to programmed cell death ligands 1 and 2 (PD-L1/2) (38). Similar to the CTLA-4 signal, activation of the PD-1 signal pathway reduces T cell proliferation and T cell survival. In addition, it inhibits interferon gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and IL-2 production (38). When TCR and PD-1 binding is seen in a T cell, the signals produced by PD-1 cause a decrease in the activation of T cells (39, 40). PD-1 expression is one of the most important distinguishing features of exhausted T cells (41). This fatigue seen during chronic infection and cancer is characterized by T cell dysfunction resulting in inadequate control of infection and tumor. Both CTLA-4 and PD-1 binding have a negative effect on T cell activation. However, the timing of downregulation, responsible signaling mechanisms, and anatomical locations distinguish these two immune checkpoint inhibitors. Unlike CTLA-4, PD-1 is mostly expressed in active T cells, B cells and myeloid cells (25, 38). While CTLA-4 functions in the priming phase of T cell activation, PD-1 functions in the effector phase (38).). B7 ligands for CTLA-4 are typically expressed by lymph nodes or professional APCs located in the spleen (25). However, PD-L1 is expressed in leukocytes, non-hematopoietic cells, non-lymphoid tissues. PD-L1 can also be induced in parenchymal cells by IFN-γ or tumorigenic signal pathways (42). PD-L1 expression has been found in many different types of tumors and is associated with an increased amount of tumor-infiltrating lymphocytes (TILs) (43-45). PD-L2 is expressed in dentritic cells and monocytes, but can be induced in other immune and non-immune cells depending on the local microenvironment (46). Inhibition of PD-L2 binding causes increased TH2 activation (47) but binding of PD-L1 to CD80 has been shown to inhibit the T cell response (48). It has been reported that PD-L1 helps transformation of naive CD4+T cells into Treg cells and inhibits T cell response by stimulating the maintenance of Treg cells (49).

1.6. Solid Organ Transplant Rejection Associated with Immune-Checkpoint Inhibitors

In solid organ transplantations, the survival rate of graft has increased recently. Patients undergoing organ transplantation should use long-term immunosuppressants to balance side effects such as the risk of allograft rejection and infection. Acute rejection risk generally decreases with the time elapsed after transplantation. In this process, transplant patients need less immunosuppressor than the dose they originally used. The required level of immunosuppressant varies according to the different type of organ transplant. The general procedure applied is the combination of 2 or 3 drugs. Thus, dose-dependent side effects are minimized (50).

In the post-operative process, many patients are treated with corticosteroids. Due to the side effects of chronic steroid use, it is either gradually reduced in the first months or a permanent low (maintenance) dose is administered. Calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus block T cell activation signal-2. These agents form the basis of immunosuppressants in almost all protocols. Agents affecting the cell cycle, such as mycophenolate mofetil, are often added to the treatment protocol. Because of the nephrotoxicity associated with calcineurin inhibitors, agents that interact with the mTOR pathway such as sirolimus and everolimus are used (51). However, chronic immunosuppressive treatments applied to organ transplant patients have been reported to be associated with malignancies which involve increased de novo non-melanoma skin cancer, malignant melanoma, lymphoma, kidney, head and neck cancer, choleratal cancer and lung cancer (52-55). The use of immune checkpoint inhibitor antibodies such as CTLA-4 and PD-1 in small cell lung cancer, melanoma and renal cell cancer has been reported to provide long-term stabilization and tumor regression effects (56, 57). However, it is thought that the use of these inhibitors may be associated with increased graft rejection. Blocking CTLA-4 and PD-1 increases the activation of T cells. Activation of T cells is not only against malignant cells but also against other cells expressing foreign antigens such as kidney allograft donor antigens. This T cell activation can cause acute cellular rejection, and active CD4+T cells can stimulate the proliferation and activation of B cells through co-stimulatory ligands such as CD40 and cytokines such as IL-4, IL-21, and IFN-γ that cause antibody-mediated rejection (58). If there is a decrease in

immunosuppressive drugs or transplanted organ sensitization, B cells can act directly on memory B cells expressing PD-1. Management of melanoma in kidney transplant patients includes aggressive reduction in immunosuppressant medications, which are tailored based on the patient's age, HLA compliance, time after transplantation, and a history of rejection (53). In studies, it has been reported that the time to start applying the immune checkpoint inhibitor therapy for cancers seen after transplantation is average 12.5 years (51). While melanoma patients with a history of allograft rejection take prednisone only, patients without a history of rejection complete their treatment with immunosuppressants such as tacrolimus, mycophenolate mofetil or cyclosporine (59-62).

1.7. Use of Ipilimumab for Renal Transplant Patients with Advanced Cancer

Ipilimumab: It is a fully humanized monoclonal antibody that acts directly against CTLA-4, a member of the CD28-B7 superfamily. CTLA-4 activation reduces CD4+T helper cell activity and induces immune tolerance by increasing the function of CD4+T regulatory cells (Treg) (63). Ipilimumab blocks the inhibitory T cell signal by binding to CTLA-4. It was approved by the FDA in 2011 for use in the treatment of patients with metastatic melanoma that cannot be surgically removed. It resulted in durable clinical response in patients with metastatic malignant melanoma (64). Phase III studies have reported that ipilimumab increases the survival rate compared to dacarbazine or peptide vaccine control (64, 65). Since Ipilimumab blocks CTLA-4, the activity of T cells against donor antigens expressed by cancer cells and allografts of solid organ transplantation patients increases. The primary event in acute kidney transplantation rejection is the recognition of donor antigens by T cells. Full activation of T cells is completed by the interaction of co-stimulator molecules that bind to CD28 and its ligands (33). The risk/benefit ratio of ipilimumab in transplant patients makes the use of immune checkpoint inhibitors in transplant patients therapeutic dilemma.

Ipilimumab+PD-1 inhibitors: While CTLA-4, predominantly found in lymphoid tissues, plays a critical role in early immune response, PD-1 regulated after T cell activation in peripheral tissues plays a role in late immune response (66). The positive effect of PD-1 and ligand PD-L1 on survival with its anti-cancer activity and regulatory effect has been shown in metastatic melanoma, non-small cell lung cancer and renal cell carcinoma (56, 57). Blocking these pathways with anti-CTLA-4, anti-PD-1 and anti-PD-L1 antibodies help maintain the anti-tumor properties of T cells (57, 64, 66). PD-1 inhibitors such as nivolumab and pembrozulimab have been shown to have a far greater effect than ipilimumab in metastatic melanoma. However, due to similar therapeutic mechanisms, both nivolumab and pembrolizumab applications can result in allograft rejection. It has been reported that the risk of rejection posed by PD-1 inhibitors after transplantation is higher than CTLA-4 antagonists (67). Blocking PD-1-PD-L1 interaction in kidney tubular cells may impair FoxP3+regulatory T cell-mediated graft tolerance (68). In some studies, it has been reported that glucocorticosteroid administration may impair the anti-tumor response of immune checkpoint inhibitors (69). It is recommended to use anti-CTLA-4 agents in solid organ transplantation patients compared to PD-1 because CTLA-4 receptors are non-peripheral tissue-specific mechanism and the risk of acute rejection of allograft is lower. Ong et al. (60) suggested that patients with high rejection risk can be classified by characterizing PD-L1 expression on the renal allograft before applying the anti-PD-1 agent. Although there is no study on this subject, it has been reported that T cells expressing PD-1 may be a marker for the risk of renal transplant rejection (70). There are ideas that PD-1 inhibitors are beginning to replace ipilimumab monotherapy due to the increased risk/benefit ratio. Therefore, the combination of both is considered as an alternative treatment method (71).

2. Discussion

Allogeneic kidney transplantation is a good option for end-stage kidney patients in relation to increased quality of life and survival. These patients use long-term immunesuppressants to reduce the risk of acute rejection, maintain the transplanted organ and increase renal function. The development of immunosuppressive drugs plays a key role in suppressing allograft rejection. With its increasing immunosuppressive activity, acute rejection incidence decreases significantly. However, increased immunosuppressive effect brings with it increased infection and malignancies after transplantation. The risk of cancer developing after transplantation is 3-5 times higher when compared to the general population (72).

Developments in cancer therapy are increasing day by day. One of them is immunotherapy. The use of immunotherapy in cancer treatment brings different side effects. Immune checkpoint inhibitors act by modulating the co-inhibitor T cell signal (73). Immune checkpoint inhibitors targeting CTLA-4 and PD-1 have been used in many types of cancer. The CTLA-4 pathway plays a key role in suppressing the immune response and tolerating itself (74). CTLA-4 blockade has been reported to increase the anti-tumor response with the study in the mouse model (75). Tivol ve ark (76) reported that CTLA-4 deficient mice are susceptible to autoimmune infiltration and organ damage. In addition, antibodies used against CTLA-4 receptors in mouse cardiac transplant patients have been reported to accelerate acute cellular rejection and graft loss (77, 78). CTLA-4 antagonists have the

potential to trigger rejection events in transplant patients (79). Based on all these data, the high risk of graft rejection due to chronically used immunosuppressors in organ transplant patients limits the use of immune checkpoint inhibitors.

Ipilimumab is a fully humanized monoclonal antibody that acts directly against CTLA-4. Ipilimumab blocks the inhibitory T cell signal by binding to CTLA-4. It was approved by the FDA in 2011 for use in the treatment of patients with metastatic melanoma that cannot be surgically removed. CTLA-4 activation reduces CD4+T helper cell activity and induces immune tolerance by enhancing the function of CD4+T regulatory cells (Treg) (63). CD28-B7 (CD80) interaction which is blocked by using CTLA-4-Ig in mice has been reported to reduce IgA accumulation, mesengial proliferation and proteinuria level. These studies provide evidence that the reduction or exacerbation of IgA nephropathy is a potential complication of ipilimumab therapy (80).

In the literature, it has been reported that the ratio between ipilimumab monotherapy applied to organ transplant patients and organ rejection is low (23%, 3/13 patients) but not insignificant (8, 81-84). The risk/benefit ratio of ipilimumab during treatment in these patients is controversial.

Since it has little effect on the control of oncological diseases, it is believed that the dose of immunosuppressant should not be reduced before the use of an immuno-checkpoint inhibitor to minimize the risk of renal transplant rejection (85). Immune checkpoint inhibitor deficiency is thought to be effective rather than immunosuppressant deficiency in the progression of melanoma (85). However, it is believed that the effect of ipilimumab used with an immunosuppressive agent such as rapamycin to prevent graft rejection during treatment may vary depending on the immunosuppressive and dose used (81). Similarly, Alhamad et al. (61) reported that ipilimumab, which was applied for the treatment of metastatic melanoma seen in the renal transplant patient after transplantation, improved kidney function, but the patient resulted in hemodialysis. Conversion of tacrolimus's rapamycin inhibitors to mammalian target and increased dose of prednisone are thought to be an alternative solution for preventing rejection.

Lipson et al. (8) reported that ipilimumab treatment which is used for post-transplant melanoma in renal transplant patients treated with ipilimumab did not cause graft rejection and graft functions continue normally. It is thought that rejection is not seen due to the fact that the treatment is performed many years after the transplant, these patients need low dose prednisone to maintain their renal function and the body accepts graft after all. The activation and expression of donor antigens may vary in patients. The balance between Treg and effector T cells may differ between different anatomical compartments such as peripheral blood, tumor and allograft. This variation is another way of explaining that allograft function is not impaired despite the use of ipilimumab in 2 patients (86). Based on all this, Lipson et al. (8) suggested that ipilimumab can be a safe option for the treatment of post-transplant melanoma in patients who had solid organ transplantation. Similarly, Ranganath et al. (83) reported that graft rejection was not observed in the patient who underwent liver transplantation with ipilimumab treatment for malignant melanoma seen after transplantation.

In the case reports, Zehou et al. (85) reported that only one of the patients had acute graft rejection after the first ipilimumab injection in the case of reduced immunosuppressants. Therefore, each factor causing rejection could not be clearly defined. Current immune checkpoint inhibitor strategies are based on anti-PD-1 alone or in combination with ipilimumab. Considering the risk of organ rejection, ipilimumab has been reported to be safer than anti-PD-1. However, the immune checkpoint inhibitor combinations planned to be applied in the evaluation of the tolerance to the transplanted organ need to be well documented (85).

Spain et al. (59) reported that the PD-1 inhibitor nivolumab used in the treatment of malignancy developed after transplantation in renal transplant patients, besides ipilimumab, showed graft loss due to secondary acute rejection in the patient. It is believed that these agents are applied consecutively in a short time leads to an increase in T cell activation beyond induced by ipilimumab alone, and the risk of toxicity associated with immunity may be increased.

PD-1 inhibitor nivolumab, used for the treatment of invasive melanoma after renal transplantation, has been reported to cause impaired renal allograft functions and results in hemodialysis. The immune checkpoint blockade applied to solid organ transplant patients is considered to be more dangerous than non-renal transplant patients (60).

The use of mTOR inhibitors for immunosuppression has been shown to further reduce the risk of malignancy compared to calcineurin inhibitor-based regimens (87). However, most renal transplant patients with intact graft integrity are applied treatments combined with immunosuppressive drugs or mTOR inhibitors. It is thought that low dose steroids and mTOR inhibitors given during anti-PD-1 inhibitors, which are used for anti-tumor treatment in renal transplant patients, prevent graft rejection (88). Barnett et al. (89) administered PD-1 inhibitor nivolumab for use in the treatment of metastatic adenocarcinoma after transplantation in a renal transplant patient. It is thought that glucocorticoid and sirolimus (a mammalian target of rapamycin [mTOR] inhibitor) applied to the patient during the treatment prevent the adverse effect of nivolumab and sirolimus may have synergistic antitumor effect in addition to being an immunosuppressive agent.

Local immunomodulatory strategies theoretically increase the anticancer response without affecting the risk of rejection. The immune-modulating effect of radiotherapy as well as the use of immune checkpoint

inhibitors has been demonstrated in many preclinical and clinical studies. Radiation can trigger the release of antigens from the tumor by inducing antitumor immune response (90). Many studies have shown that immunotherapy can increase this effect (91-93), and recent phase I studies have reported that the combination of radiotherapy and immunomodulator has different clinical outcomes (94). If synergy between radiotherapy and checkpoint inhibitors is approved for many malignancies, it may be an alternative option for use in transplant patients with cancer development.

Although allograft kidney transplantation is a good option for end-stage kidney patients, immunosuppressants, which are used chronically to prevent graft rejection, can cause various malignancies in the long term. Today, different protocols are applied to these patients with many alternative treatment methods. Although the use of immune checkpoint inhibitor is one of these methods, the risk/benefit ratio is controversial.

3. Conclusion

The immune checkpoint inhibitor treatment protocol applied according to the duration after the transplant in the treatment process, the improvement in kidney functions, the level of donor antigens' expression, the immunosuppressants used and malignancy, affects the renal survival rate. Although the exact solution cannot be fully provided, new treatment protocols and combinations need to be developed.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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