ELMER PRESS

Review

J Clin Med Res. 2024;16(12):571-577

# Clinical Implications of Skin Cancer in Kidney Transplant Recipients in the Era of Immune Checkpoint Inhibitors

Lakshmi Manogna Chintalacheruvu[a, c, d], Vamsi Krishna Chilluru[b, c]

## Abstract

Long-term survival has improved in kidney transplant recipients (KTRs) due to effective surgical techniques and anti-rejection therapies. Chronic immunosuppression associated with it has led to several types of skin cancers leading to substantial morbidity and mortality. Structured patient education including sun protective behaviors, regular dermatological surveillance, nicotinamide, long-chain omega-3 polyunsaturated fatty acids (PUFAs), early switch to mammalian target of rapamycin inhibitors (mTORis), combining them with low-dose calcineurin inhibitors (CNIs), can decrease the cancer risk. Checkpoint inhibitors (CPIs) are the major backbone of the treatment of advanced skin cancers. Unfortunately, these agents can increase the risk of graft rejection. Prospective studies done so far looking at combining steroids with CPI in treatment of skin cancer in KTRs have shown mixed results. Adoption of the weight-based approach of CPI has shown to decrease the amount of drug exposure with acceptable outcomes in the general population, which is something that can be studied in KTRs with skin cancer. Also, it is reasonable to consider surveillance allograft biopsies in KTRs receiving CPIs to detect early subclinical rejection. More studies are needed to develop guidelines to safely treat this population with minimal graft rejection. We conducted a comprehensive literature review from PubMed on skin cancer in kidney transplant patients, focusing on incidence, risk factors, protective behaviors, financial and treatment implications, especially with regards to CPIs therapy. We also discussed potential newer treatment options that will decrease skin cancer risk, as well as graft rejection.

**Keywords:** Kidney transplant; Skin cancer and prevention; Immunosuppression; Immune checkpoint inhibitors

## Epidemiology

Long-term survival has improved in kidney transplant recipients (KTRs) over many years due to effective surgical techniques and anti-rejection therapies [1]. But chronic immunosuppression associated with it has led to several types of cancers including skin cancer leading to substantial morbidity and mortality [2]. Types of skin cancer among them include squamous cell carcinoma (SCC), basal cell carcinoma (BCC), Merkel cell, malignant melanoma, cutaneous lymphoma and Kaposi sarcoma [2]. In a retrospective study done at a single tertiary care academic medical center in the USA, which included 5,129 solid organ transplant recipients who underwent transplant surgery between 1992 and 2017, they found 695 patients (13.6%) had development of at least one skin cancer, with 6,842 skin cancers identified in the overall cohort [3]. In comparison to liver transplant recipients, KTRs are more likely to develop at least one skin cancer [3]. The mortality rates due to SCC, BCC and malignant melanoma are 23.8%, 18% and 41.6%, respectively, which are significant [4].

## Risk Factors

One of the major risk factors for skin cancer in KTRs is ultraviolet (UV) light exposure, which induces DNA damage. This, combined with severe immunosuppression, leads to the reactivation of oncogenic viruses [2]. Other risk factors include age at transplantation, smoking, male sex, and viral infection with human papillomavirus (HPV), previous history of skin cancer, fair skin complexion and autosomal dominant polycystic kidney disease [5, 6]. In a single-center study performed in Poland among KTRs, they found that human leukocyte antigen (HLA)-DR 15 is more commonly detected in patients with non-melanoma skin cancer (NMSC), and a similar correlation was found between HLA-B18 and skin SCC [7]. This raises the question of whether more research is needed in this area to see if these patients need close dermatological surveillance [7].

Hydrochlorothiazide (HCTZ) is a diuretic usually recommended as first-line treatment for essential hypertension [8]. HCTZ contains sulfonamide moiety, which under UV light exposure, becomes activated and gets converted into reactive oxygen species [8]. In a retrospective study consisting of 520 patients, exposure to higher cumulative doses of HCTZ during post-transplant was associated with an increased risk of BCC but with no significant association to SCC [8]. The European Medicines Agency and the US Food and Drug Administration issued recommendations advising patients using HCTZ to be informed about the risk of NMSC and to undergo regular skin checkups [8]. In another meta-analysis performed by Shao et

Manuscript submitted October 9, 2024, accepted December 2, 2024
Published online December 20, 2024

[a]Hematology/Oncology, Southern Illinois Health Cancer Institute, Carterville, IL, USA
[b]Nephrology, Southern Illinois Health, Carbondale, IL, USA
[c]Both authors contributed equally to this manuscript.
[d]Corresponding Author: Lakshmi Manogna Chintalacheruvu, Hematology/Oncology, Southern Illinois Health Cancer Institute, Carterville, IL, USA. Email: lakshmikrishna365@gmail.com

doi: https://doi.org/10.14740/jocmr6088

al, which looked at association of thiazide drug use and skin cancer, they found associations of HCTZ use with increased risks of NMSC (odds ratio (OR): 1.16, 95% confidence interval (CI): 1.08 - 1.24; hazard ratio (HR): 1.26, 95% CI: 1.04 - 1.54), SCC (OR: 1.32, 95% CI: 1.06 - 1.65; HR: 1.61, 95% CI: 0.97 - 2.67), and melanoma (OR: 1.11, 95% CI: 1.02 - 1.20; HR: 1.03, 95% CI: 0.93 - 1.14) [9]. The increased risks for SCC were associated with high cumulative doses of HCTZ (OR: 2.56, 95% CI: 1.43 - 4.57; HR: 1.20, 95% CI: 1.00 - 1.45) [9]. However, the associations of HCTZ use with increased risk of NMSC and melanoma only appeared in non-Asian countries [9]. More research needs to be done regarding implications of medications in the incidence of skin cancer in KTRs [9].

## Financial Implications

Skin cancer in KTRs can lead to significant financial burden [10]. Indirect costs associated with premature morbidity and mortality due to skin cancer in KTRs was $28.9 - 39.2 million and $1.0 - 3.3 billion, respectively in the USA, Canada, Brazil, Australia, New Zealand, and European countries [10]. In a study looking at Medicare-insured KTRs in the USA between 2000 and 2011, it showed that skin cancer accounted for 3-5.5% of inpatient Medicare expenditure and 1.5-3.3% of outpatient expenditures in the first 3 years post-transplant [11]. In another study conducted by Thet et al, they found a total of 231 visits to clinicians for diagnostic and therapeutic skin procedures and the direct costs to Medicare was 48,806 Australian dollars (AUD) or $30,427 [12]. This above data provide insight into the increasing clinical and economic burden of the care for benign and malignant skin lesions in the renal transplantation setting worldwide [12].

## Practices to Decrease the Risk

Since prevention is always better than cure, what can we do to decrease the incidence of skin cancers? Patient education regarding the practices below plays a major role in achieving this.

### Sun protective behaviors

The rationale behind this is that it decreases UV light exposure and avoids further skin damage [10]. Educating patients regarding regular self-exam, dermatological follow-up, providing a booklet to understand skin cancer, and teaching protective practices will decrease the risk of skin cancer [10]. It is also important to discuss with the patient to understand the barriers that facilitate the practice of sun protective behaviors [10]. Studies have shown that this practice has improved skin checkups to 92% at 3 months post education [10]. It is not only important to improve these numbers but also to maintain that for consistent and better results over the long time [10]. We also need more recommendations and guidelines on the optimal timing to provide follow-up skin cancer education to patients [5]. Literature reviews have shown the low level of sunscreen use among KTRs and their scanty awareness of personal skin cancer risk [13]. Since educational level has been found to be highly related to both awareness of cancer risk and adequate use of sunscreen among KTRs, it is necessary to improve the way education is delivered by dermatologists, primary care physicians and nephrologists, especially to subjects with a low educational level [13].

### Immunosuppression

Calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, are effective immunosuppressants used in prophylaxis and treatment of graft rejection following organ transplantation [10]. These are known to contribute to an increased incidence of secondary skin cancer by inhibition of cyclosporin A, which results in activation of transcription factor 3 (ATF3) [10]. ATF3 downregulates *p53* gene expression by negative regulation of the *p53* messenger ribonucleic acid (mRNA) expression and is also known to increase formation of SCC in mice and humans [10]. While immunosuppression is required to prevent post-transplant rejection, other treatment modalities have been studied like mammalian target of rapamycin inhibitors (mTORis), which includes everolimus and sirolimus [10]. mTORis are macrolide antibiotics that have immunosuppressive, anti-fungal, and anti-neoplastic properties [10]. Studies have shown that mTORi shows a renoprotective effect and prevents chronic allograft nephropathy [10]. This makes them a good alternative immunosuppressant in KTRs [10].

In that regard, multiple studies have examined switching from CNIs to mTORis after skin cancer was diagnosed in KTRs [6]. In a randomized controlled trial performed by Salgo et al, which looked at 44 KTRs who either continued previous immunosuppressive medication (n = 19) (azathioprine/mycophenolate, cyclosporine or tacrolimus) or switched to sirolimus (n = 25), it has shown that conversion to sirolimus inhibited the progression of pre-malignancies and significantly decreased the number of patients who developed histologically confirmed NMSC (6.3% vs. 47.1%; P = 0.017). Another interesting observation is that the sirolimus group showed a high discontinuation rate of 36% compared to 11% in the control group [14].

Ying et al did a meta-analysis including four randomized, prospective studies involving Australian and New Zealand participants, which compared standard triple therapy (cyclosporine or tacrolimus, mycophenolic acid, and corticosteroids which is control group) to *de novo* or conversion from CNI to everolimus within 6 months after kidney transplantation [15]. They included 279 patients in the study (192 everolimus, 87 control), with a median follow-up of 9 years [15]. They found that compared with control group, everolimus use was not associated with a reduction in the risk of incident cancer, NMSC, or cancer-related death (unadjusted HR (95% CI): 0.86 (0.49 - 1.48), 0.58 (0.30 - 1.12), and 1.18 (0.32 - 4.38), respectively) [15]. Interestingly, subgroup analyses showed a 56% reduction for NMSC in patients randomized to everolimus + reduced-dose CNI versus control (unadjusted HR: 0.44 (0.21 - 0.92)),

 

which remained significant even after adjusting for age, gender and smoking (adjusted HR: 0.45 (0.21 - 0.96)) [15]. They found that *de novo* or early switch to everolimus did not alter the 9-year risk of incident cancer or cancer-related death, but everolimus with reduced-dose CNI strategy may reduce the long-term risk of NMSC [15]. More studies are required to affirm this.

Belatacept is a cytotoxic T lymphocyte associated protein 4 (CTLA-4) fusion antibody, which is an immunosuppressant and is approved for use after kidney transplantation [16]. In a retrospective study done at Yale New Haven Hospital, looking at skin cancer risk in KTRs after being switched to belatacept from CNI, switching to belatacept was associated with increased SCC-free survival with similar rates of death and graft loss and improved renal function compared to CNI. So, belatacept has the potential to be first-line immunosuppressive agent instead of CNI in KTRs, and more prospector trials are warranted to further explore this [16].

### Nicotinamide

Nicotinamide is a precursor of nicotinamide adenine dinucleotide (NAD+), which has been reported to be effective in reducing the rates of new NMSC and actinic keratoses (AKs) [17]. In a study conducted in Italy, where they recruited 30 kidney transplant patients and eight liver transplant patients with single or multiple AKs, 19 patients were randomly assigned to group 1 and took nicotinamide 500 mg/daily, and the other 19 patients were randomly assigned to group 2 without nicotinamide (controls) [17]. At baseline, no statistically significant differences were observed regarding AKs size between the two groups; and after 6 months, AKs had significantly decreased in size in 18/19 patients in the intervention group (88%) [17]. Conversely, among the control group, 91% showed an increase in AKs size and or developed new AKs. Seven pre-existing AKs progressed to SCC among these patients [17]. Although this is not a large study, it has definitely shown some meaningful improvement and needs to be tested in a larger group [17].

### Long-chain omega-3 polyunsaturated fatty acids (PUFAs)

A study was conducted in 449 adult kidney or liver transplant recipients, who had been transplanted for at least 1 year and were at high risk of skin cancer. The study was done at the main transplant hospital in Queensland (2012 - 2014), with follow-up until mid-2016 [18]. They estimated their dietary total PUFAs and α-linolenic acid intakes at baseline using a food frequency questionnaire and ranked PUFA and α-linolenic acid intakes as low, medium, or high [18]. Relative risks of skin cancer adjusted for confounding factors with 95% CIs were calculated. During follow-up, 149 (33%) patients developed SCC (median: 2/person; range: 1 - 40), and 134 (30%) patients developed BCC. Transplant recipients with high total long-chain omega-3 PUFA intake compared with low intakes showed substantially reduced SCC tumor risk (adjusted relative risk (RR adj): 0.33, 95% CI: 0.18 - 0.60), and those with high α-linolenic acid intakes experienced significantly fewer BCCs (RR adj: 0.40, 95% CI: 0.22 - 0.74) [18].

There are various prospective studies going on now investigating strategies to decrease the risk of rejection in transplant recipients receiving CPIs. These include "Immune checkpoint inhibitors in kidney transplant recipients: a multicenter, single-arm, phase 1 study" [19] (NCT0589369) and "Immunotherapy in combination with prednisone and sirolimus for kidney transplant recipients with unresectable or metastatic skin cancer" [20]. Hopefully, results from these studies will shed light on the mechanism of skin cancer and strategies to mitigate the risk in KTRs treated with CPIs.

## CPIs in Advanced Skin Cancer

### Introduction

T lymphocytes play a major role in anti-tumor response and allograft rejection [21]. Major histocompatibility complex (MHC) is involved in antigen presentation to the T cell receptor (TCR) on T cells [21]. Following the antigen presentation, further T cell activation happens by binding of CD28 to CD80 and CD86 and creating a co-stimulatory signal on antigen presenting cells (APCs) [21]. Interaction of T cells with co-stimulatory molecules is tightly regulated by inhibitory checkpoints to avoid auto immunity and immune dysregulation [21]. Checkpoint molecules include lymphocyte activation gene 3 (LAG3), programmed cell death protein 1 (PD-1 and CTLA-4 [22]. Interaction of PD-1 on T cells and programmed cell death ligand 1 (PD-L1) on tumor cells mediate immune escape of tumor cells in the microenvironment [21], whereas CTLA-4 is present proximally at the T-cell priming sites and limits T-cell activation in secondary lymphoid organs [21]. This has led to the idea of producing immune CPI to see if it can activate the immune system to kill the tumor cells [20]. Since then, CPIs have revolutionized cancer treatment [21].

CPIs, such as ipilimumab, nivolumab, pembrolizumab, cemiplimab, are the backbone of treatment for the majority of advanced skin cancers, including melanoma, SCC, and Merkel cell carcinoma, as mentioned in Table 1 [21]. Incidence of advanced skin cancer in KTRs can make treatments challenging, as CPIs are the backbone of these treatments, which can cause graft rejection [21].

### Mechanism of allograft rejection with CPIs

Mechanism of allograft rejection in KTRs due to CPIs is not clearly understood.

According to an observational study conducted by Dunlap et al, they found that alloreactive T cells are present in the KTRs despite being on immunosuppression for a decade, more likely due to a combination of immune tolerance mechanism and immunosuppression [23]. Sometimes immunosuppression has to be decreased at times to avoid interaction with CPIs, which plays a role in rejection of the graft.

**Table 1.** Food and Drug Administration-Approved Indications of CPIs in Skin Cancer Patients

| Drug | Target | Indications | Year of approval |
|---|---|---|---|
| Ipilimumab | CTLA-4 | Melanoma | 2011 |
| Nivolumab | PD-1 | Melanoma, SCC of head and neck | 2014 |
| Pembrolizumab | PD-1 | Melanoma, Merkel cell carcinoma, cutaneous SCC | 2014 |
| Atezolizumab | PD-L1 | Melanoma | 2016 |
| Avelumab | PD-L1 | Merkel cell carcinoma | 2017 |
| Cemiplimab | PD-1 | Cutaneous SCC, BCC | 2019 |
| Relatlimab | LAG-3 | Melanoma | 2022 |

SCC: squamous cell carcinoma; BCC: basal cell carcinoma; CPIs: checkpoint inhibitors; CTLA-4: cytotoxic T lymphocyte associated protein 4; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; LAG-3: lymphocyte activation gene 3.

Preclinical studies have shown that PD-1/PD-L1 pathway has a role in immune tolerance [21]. Blockade of PD-1/PD-L1 pathway by CPIs not only affects the immune tolerance but also has known to show expansion of alloreactive effector $CD8^+$ cells, Th1 differentiation of $CD4^+$ T cells, and decrease in Foxp3 $CD4^+$ $CD25^+$ T-cell infiltration in affected grafts. This leads to accelerated rejection of the graft in KTRs [21]. Also, KTRs with allograft rejection have an upregulation of tissue *PD-L1* mRNA, which points towards potential protective effect of PD-L1 during immune activation [21].

KTRs patients started on CPIs, despite being on immunosuppression, may experience activation of alloreactive T cells resulting in increased circulation of these cells in the circulation and allograft leading to graft rejection [23]. $CD8^+$ T cells in the kidney allograft of a patient treated with CPIs had a specific transcriptome profile [21]. They were noted to express ZNF683, CXCR3, and HLA-DR, which had not been noted in the tumor cells [21]. Rejection has been noted to be the highest under anti-PD-1 therapy compared to anti CTLA-4 therapy [21]. Another possible mechanism is that tumor can also have immunosuppressive effects on the host by releasing adenosine, prostaglandin E2, transforming growth factor (TGF) beta 1, while tumor shrinkage by CPIs can indirectly accelerate host responses towards the allograft.

## Strategies to decrease the risk of graft rejection while on CPIs

Two prospective trials were published this year to guide the management of CPIs in KTRs with cutaneous malignancies. One of them is the CONTRAC-1 trial, which investigated the use of an mTORi along with pulsed dose corticosteroids and cemiplimab in 12 KTRs [24]. They received prednisone taper each cycle (40 mg on day 1 - 3, 20 mg on day 4 - 6, and 10 mg on day 7 - 20), along with cemiplimab, which is a CPI at the dose of 350 mg intravenously every 21 days [24]. The response rate was comparable to that found in the general population, which is close to 50% [24, 25]. In addition, there was no reported rejection among the patients [24]. Another prospective study was conducted by Schenk et al, which tested nivolumab plus tacrolimus (serum trough 2 - 5 ng/mL), prednisone (5 mg daily) with or without ipilimumab in KTRs with advanced cutaneous cancer [26]. They included patients with advanced melanoma or BCC, cutaneous SCC, or Merkel cell carcinomas [26]. Unfortunately, all eight patients experienced disease progression and also were found to have elevated donor-derived cell-free DNA (dd-cfDNA), which were proposed to be an early marker of allograft rejection [26]. This showed that tacrolimus and prednisone hindered the tumor response of CPIs while not being effective in providing protection against allograft rejection [26]. Although these two studies mentioned in Table 2 [24, 26] had conflicting results, these should be interpreted with caution, as the choice of CPIs used and types of skin cancers were different, sample size was small with no control arm [27]. These two studies did not include surveillance allograft biopsies, which could have detected early subclinical rejection. It would be reasonable to include this approach in future studies [27].

Another debatable question these days is regarding the optimal dosing of CPIs [28]. In the initial phase 3 registration trials of pembrolizumab and nivolumab, per-weight (mg/kg) dosing was used, but later, fixed doses became the norm in clinical trials [28]. These doses are much higher than those needed to inhibit the target PD-1 or PD-L1 [28]. For example, in a phase 1 trial conducted by Robert et al, patients with melanoma whose disease had progressed after at least two ipilimumab doses were studied [29]. They allocated these patients with a 1:1 schedule of intravenous pembrolizumab at either 2 mg/kg every 3 weeks, or 10 mg/kg every 3 weeks, while the standard dose of pembrolizumab used currently is 300 mg every 3 weeks [29]. They found that the overall response rate (ORR) was similar, around 26%, for both doses [29]. Ribas et al also tested various dosing regimens of pembrolizumab with 2 mg/kg once every 3 weeks and 10 mg/kg once every 3 weeks in 540 patients with ipilimumab-refractory melanoma [30]. They found that progression-free survival (2.9 vs. 2.9 months), and ORR (21% vs. 26%) were similar in both groups [30].

In a retrospective study conducted by Qian et al looking at the effect of immunotherapy infusion time of day on survival of patients with advanced melanoma, they looked at the database for adults aged more than 18 years diagnosed with stage 4 melanoma between 2012 and 2020 [28]. They found that patients receiving immunotherapy after 4:30 pm had at least 20% less overall survival compared to people who received the

 

**Table 2.** Prospective Studies of CPIs in KTRs With Skin Cancers

| Study | Schenk et al, 2024 [26] | Hanna et al, 2024 [24] |
|---|---|---|
| Number of KTRs enrolled | 8 | 12 |
| Median age | 66 | 62 |
| Cancers included | Advanced melanoma (1), cutaneous SCC (5), Merkel cell carcinoma (2) | Advanced cutaneous SCC |
| CPIs used | Nivolumab (480 mg IV every 4 weeks) in all patients initially, in six out of eight patients with disease progression, ipilimumab (IPI) (1 mg/kg, IV) + nivolumab (NIVO) (3 mg/kg IV every 3 weeks, four times), followed by NIVO | Cemiplimab (350 mg IV every 3 weeks) |
| Median time from transplantation to start of CPIs | 13 years | 7.2 years |
| Primary endpoint | Disease control rate (complete response (CR), partial response (PR), or stable disease), allograft loss at 16 weeks | Rejection or allograft loss |
| Median follow-up time | 9.1 months | 6.8 months |
| Safety outcomes | Three of eight patients experienced TRAL; excluding TRAL, no grade 3 or higher TRAE related to IPI + NIVO. | No patients had rejection or allograft. TRAE occurred in 83% (grade 3 or higher in 42%). |
| dd-cfDNA | Performed every 2 weeks in all patients and weekly if rising; increased 10 - 15 days before rise in serum creatinine. | Performed in five patients at baseline and after cemiplimab; minor increase in only one. |
| Conclusions | Tacrolimus and prednisone decrease tumor response with no protection on rejection. | Cemiplimab had a response rate similar to general population, and use of mTORi along with pulse-dose steroids had acceptable safety profile and rejection rate. |

KTRs: kidney transplant recipients; SCC: squamous cell carcinoma; CPIs: checkpoint inhibitors; dd-cfDNA: donor-derived cell-free DNA; IV: intravenous; TRAL: treatment-related allograft loss; TRAE: treatment-related adverse event; mTORi: mammalian target of rapamycin inhibitor.

treatments prior to that [28].

A possible explanation would be that adaptive immune responses are less robust in the evening than in the early hours [28]. They recommended that more efforts should be made scheduling infusions before midafternoon to increase immune responses in advance melanoma [28]. So, more studies are needed to be done in KTRs diagnosed with melanoma and other skin cancers, to see if these patients can be treated with weight-based approach preferably in the morning to achieve adequate treatment response while minimizing the graft rejection.

Interleukin-6 (IL-6) is a cytokine important for innate and adaptive immune responses [31]. It may play a role in both cell-mediated and antibody-mediated rejection [31]. Data from clinical trials and observational studies show that tocilizumab (anti-interleukin-6 receptor (IL-6R)) and clazakizumab (anti-IL-6) may have a role in the treatment of cell-mediated and antibody-mediated rejection [29]. This has led to a phase 3 placebo, randomized clinical trial (IMAGINE) of clazakizumab for treatment of cell-mediated rejection, for which there is currently no treatment [31]. Literature review shows that anti-IL-6/IL-6R treatments have shown the ability for prevention and treatment of donor-specific antibody and allograft rejection [31]. It has also been shown that adding IL-6 inhibitors to CPIs enhances the activation of anti-tumoral immune response [31]. If results of IMAGINE trial show positive outcome, anti-IL-6 molecules can become an attractive immunosuppressive drug for KTRs requiring CPIs, for better tumoral response while minimizing graft rejection.

## Conclusions

Renal transplantation is definitely a life saver in patients with end-stage renal disease. But chronic immunosuppression increases the risk of various cancers including skin cancer which increases morbidity and mortality with economic implications as well. Structured patient education including various practices as mentioned above plays a major role in decreasing the incidence of skin cancer in KTRs. Nevertheless, the majority of clinical trial results indicate a clinical benefit from the conversion to a mTORi regimen or combination of it with low-dose CNIs in patients with low tumor burden in the early stage of disease. These patients are at increased risk of metastasis where CPI is the major backbone of the treatment. Unfortunately, these agents can increase the risk of graft rejection which poses a challenge to physicians in treating this subgroup of patients. Monoclonal antibodies against IL-6 are currently being tested in KTRs with chronic antibody-mediated graft rejection, which are also known to have anti-tumoral response. This makes them an attractive immunosuppressive option in KTRs requiring CPIs therapy. Prospective studies done so far looking at combining steroids with CPIs in treatment of skin cancer in KTRs have shown mixed results. More studies are needed to standardize optimal immunosuppressive regimen,

dosage, and timing of treatment of CPIs to improve overall outcomes in this high-risk patient subgroup.

## Acknowledgments

None to declare.

## Financial Disclosure

The authors declare that they do not have a financial relationship with any commercial entity that has an interest in the subject of this manuscript.

## Conflict of Interest

The authors declare that they do not have any conflict of interest.

## Author Contributions

Lakshmi Manogna Chintalacheruvu: designing the concept, literature search, data analysis and writing the manuscript. Vamsi Krishna Chilluru: literature search, analysis, writing the manuscript.

## Data Availability

The authors declare that data supporting the findings of this study are available within the article.

## Abbreviations

KTRs: kidney transplant recipients; SCC: squamous cell carcinoma; BCC: basal cell carcinoma; HPV: human papillomavirus; PUFAs: polyunsaturated fatty acids; CNI: calcineurin inhibitor; CPIs: checkpoint inhibitors; UV: ultraviolet; NMSC: non-melanoma skin cancer; HCTZ: hydrochlorothiazide; AUD: Australian dollar; ATF3: activation of transcription factor 3; mRNA: messenger ribonucleic acid; mTORi: mammalian target of rapamycin inhibitor; NAD+: nicotinamide adenine dinucleotide; AKs: actinic keratoses; CTLA-4: cytotoxic T lymphocyte associated protein 4; MHC: major histocompatibility complex; TCR: T cell receptor; APC: antigen presenting cell; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; LAG-3: lymphocyte activation gene 3; TGF: transforming growth factor; dd-cfDNA: donor-derived cell-free DNA; ORR: overall response rate; IL-6: interleukin 6

## References

1. Kang W, Sampaio MS, Huang E, Bunnapradist S. Association of pretransplant skin cancer with posttransplant malignancy, graft failure and death in kidney transplant recipients. Transplantation. 2017;101(6):1303-1309. doi pubmed
2. Ponticelli C, Cucchiari D, Bencini P. Skin cancer in kidney transplant recipients. J Nephrol. 2014;27(4):385-394. doi pubmed
3. Wheless L, Anand N, Hanlon A, Chren MM. Differences in skin cancer rates by transplanted organ type and patient age after organ transplant in white patients. JAMA Dermatol. 2022;158(11):1287-1292. doi pubmed
4. Hao X, Lai W, Xia X, Xu J, Wu Y, Lv C, Meng Q, et al. Skin cancer outcomes and risk factors in renal transplant recipients: Analysis of organ procurement and transplantation network data from 2000 to 2021. Front Oncol. 2022;12:1017498. doi pubmed
5. Thet Z, Lam AK, Ng SK, Aung SY, Han T, Ranganathan D, Newsham S, et al. An integrated skin cancer education program in renal transplant recipients and patients with glomerular disease. BMC Nephrol. 2022;23(1):361. doi pubmed
6. Olszewska B, Imko-Walczuk B, Debska-Slizien A. Non-melanoma skin cancer outcomes in kidney transplant recipients converted from calcineurin inhibitors to mTOR inhibitors: a systematic review. Postepy Dermatol Alergol. 2023;40(2):187-193. doi pubmed
7. Cegielska A, Debska-Slizien A, Moszkowska G, Imko-Walczuk B, Rutkowski B. Association between HLA type and skin cancer in kidney transplant recipients. Transplant Proc. 2016;48(5):1608-1610. doi pubmed
8. Dantal J, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, Broeders N, et al. Sirolimus for secondary prevention of skin cancer in kidney transplant recipients: 5-year results. J Clin Oncol. 2018;36(25):2612-2620. doi pubmed
9. Shao SC, Lai CC, Chen YH, Lai EC, Hung MJ, Chi CC. Associations of thiazide use with skin cancers: a systematic review and meta-analysis. BMC Med. 2022;20(1):228. doi pubmed
10. Thet Z, Lam AK, Ranganathan D, Aung SY, Han T, Khoo TK. Reducing non-melanoma skin cancer risk in renal transplant recipients. Nephrology (Carlton). 2021;26(11):907-919. doi pubmed
11. Dharnidharka VR, Naik AS, Axelrod D, Schnitzler MA, Xiao H, Brennan DC, Segev DL, et al. Clinical and economic consequences of early cancer after kidney transplantation in contemporary practice. Transplantation. 2017;101(4):858-866. doi pubmed
12. Thet Z, Lam AK, Pham T, Ng SK, Steel JC, Sawhney S, Arellano CT, et al. Clinical and economic burden of benign and malignant skin lesions in renal transplant recipients. Intern Med J. 2023;53(11):2042-2049. doi pubmed
13. Borghi A, Corazza M, Battaglia Y, Maietti E, Minghetti S, Virgili A. What is the key to improving renal transplant recipients' awareness of skin cancer risk? Dermatology. 2016;232(6):715-720. doi pubmed
14. Salgo R, Gossmann J, Schofer H, Kachel HG, Kuck J, Geiger H, Kaufmann R, et al. Switch to a sirolimus-based immunosuppression in long-term renal transplant

 

recipients: reduced rate of (pre-)malignancies and non-melanoma skin cancer in a prospective, randomized, assessor-blinded, controlled clinical trial. Am J Transplant. 2010;10(6):1385-1393. doi pubmed
15. Ying T, Wong G, Lim W, Kanellis J, Pilmore H, Campbell S, Masterson R, et al. De novo or early conversion to everolimus and long-term cancer outcomes in kidney transplant recipients: A trial-based linkage study. Am J Transplant. 2018;18(12):2977-2986. doi pubmed
16. Wang M, Mittal A, Colegio OR. Belatacept reduces skin cancer risk in kidney transplant recipients. J Am Acad Dermatol. 2020;82(4):996-998. doi pubmed
17. Drago F, Ciccarese G, Cogorno L, Calvi C, Marsano LA, Parodi A. Prevention of non-melanoma skin cancers with nicotinamide in transplant recipients: a case-control study. Eur J Dermatol. 2017;27(4):382-385. doi pubmed
18. Miura K, Way M, Jiyad Z, Marquart L, Plasmeijer EI, Campbell S, Isbel N, et al. Omega-3 fatty acid intake and decreased risk of skin cancer in organ transplant recipients. Eur J Nutr. 2021;60(4):1897-1905. doi pubmed
19. Carroll RP, Boyer M, Gebski V, Hockley B, Johnston JK, Kireta S, Tan H, Taylor A, Wyburn K, Zalcberg JR. Immune checkpoint inhibitors in kidney transplant recipients: a multicentre, single-arm, phase 1 study. Lancet Oncol. 2022;23(8):1078-1086.
20. Schenk KM. et al. Nivolumab (NIVO) + tacrolimus (TACRO) + prednisone (PRED) +/- ipilimumab (IPI) for kidney transplant recipients (KTR) with advanced cutaneous cancers. J Clin Oncol. 2022;40:9507.
21. Van Meerhaeghe T, Murakami N, Le Moine A, Brouard S, Sprangers B, Degauque N. Fine-tuning tumor- and allo-immunity: advances in the use of immune checkpoint inhibitors in kidney transplant recipients. Clin Kidney J. 2024;17(4):sfae061. doi pubmed
22. Carlino MS, Larkin J, Long GV. Immune checkpoint inhibitors in melanoma. Lancet. 2021;398(10304):1002-1014. doi pubmed
23. Dunlap GS, DiToro D, Henderson J, Shah SI, Manos M, Severgnini M, Weins A, et al. Clonal dynamics of allore-active T cells in kidney allograft rejection after anti-PD-1 therapy. Nat Commun. 2023;14(1):1549. doi pubmed
24. Hanna GJ, Dharanesswaran H, Giobbie-Hurder A, Harran JJ, Liao Z, Pai L, Tchekmedyian V, et al. Cemiplimab for kidney transplant recipients with advanced cutaneous squamous cell carcinoma. J Clin Oncol. 2024;42(9):1021-1030. doi pubmed
25. Migden MR, Rischin D, Schmults CD, Guminski A, Hauschild A, Lewis KD, Chung CH, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379(4):341-351. doi pubmed
26. Schenk KM, Deutsch JS, Chandra S, Davar D, Eroglu Z, Khushalani NI, Luke JJ, et al. Nivolumab + Tacrolimus + Prednisone +/- Ipilimumab for Kidney Transplant Recipients With Advanced Cutaneous Cancers. J Clin Oncol. 2024;42(9):1011-1020. doi pubmed
27. Attieh RM, Jhaveri KD, Wadei HM. mTOR Inhibitors and pulsed steroid regimen in kidney transplant recipients undergoing immune checkpoint inhibitor therapy for advanced cutaneous malignancies: the key toward maximizing efficacy and mitigating rejection. Kidney News. 2024;16(4):32.
28. Qian DC, Kleber T, Brammer B, Xu KM, Switchenko JM, Janopaul-Naylor JR, Zhong J, et al. Effect of immunotherapy time-of-day infusion on overall survival among patients with advanced melanoma in the USA (MEMOIR): a propensity score-matched analysis of a single-centre, longitudinal study. Lancet Oncol. 2021;22(12):1777-1786. doi pubmed
29. Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, Weber JS, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet. 2014;384(9948):1109-1117. doi pubmed
30. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, Joshua AM, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA. 2016;315(15):1600-1609. doi pubmed
31. Jordan SC, Ammerman N, Huang E, Vo A. Importance of IL-6 inhibition in prevention and treatment of antibody-mediated rejection in kidney allografts. Am J Transplant. 2022;22(Suppl 4):28-37. doi pubmed