

Transplant-Associated Skin Cancer: Role of Reducing Immunosuppression

Marcy Neuburg, MD, Milwaukee, Wisconsin

Key Words

Transplant, immunosuppression reduction, skin cancer

Abstract

This article explores the role of reducing immunosuppression as a therapeutic strategy for the problem of transplant-associated skin cancer. The specific issue of immunosuppression reduction is based on a brief historic review of the epidemiology of skin cancer in transplant patients, followed by a description of the role of immunosuppression as a cause of skin cancer. Finally, the literature pertaining to the hypothesis that reducing immunosuppression in solid organ transplant recipients favorably impacts both the incidence of cutaneous malignancy and outcomes relating to individual aggressive malignancies is presented. (*JNCCN* 2007;5:541–549)

In 1954, Dr. Joseph Murray performed the first successful kidney transplant between identical twin brothers.¹ Although this was recognized as the beginning of modern transplant medicine, it could not have occurred in the absence of parallel breakthroughs in the understanding of renal physiology, human immunology, advanced surgical techniques, and the pharmacology of antirejection agents. The initial kidney transplants used total body irradiation to suppress the host immune system. In 1960, the antimetabolite 6-mercaptopurine was found to prolong graft survival in an animal model.² The combination of 6-mercaptopurine (azathioprine) and corticosteroids became the mainstay of immunosuppressive regimens, and extended graft survival became more common. As transplant recipients experienced prolonged survival, the adverse effects of long-term immunosuppression be-

came increasingly apparent. By the mid-1960s, the increased incidence of de novo malignancies was recognized. Using an early transplant registry, Penn et al.³ first documented the elevated incidence of de novo skin cancer in transplant recipients. In 1971, these investigators reported 40 de novo tumors in renal transplant recipients, 9 of which were skin cancers.

Since this report, continued progress in immunology and antirejection pharmacology, and advances in surgical techniques and patient selection have led to the development of other solid organ transplants (e.g., heart, lung, liver, pancreas, intestines) and markedly improved graft and patient survival. Furthermore, the relationship between long-term immunosuppression in organ transplant recipients and skin cancer has been extensively documented.

This article explores the role of reducing immunosuppression as a therapeutic strategy for transplant-associated skin cancer. The specific issue of immunosuppression reduction is based on a brief historical review of the epidemiology of skin cancer in transplant patients followed by a description of the role of immunosuppression as a cause of skin cancer. Finally, the literature pertaining to the hypothesis that reduction of immunosuppression favorably impacts both the incidence of cutaneous malignancy and outcomes relating to individual aggressive malignancies is presented.

Organ Transplantation and Skin Cancer: Defining the Problem

To understand whether reducing immunosuppression plays a role in managing skin cancer in transplant recipients, the problem and population of patients who might benefit from drug-reduction strategies must be defined.

Studies aimed at defining the extent of skin cancer in organ-transplant recipients are plagued by heterogeneity

From the Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital, Milwaukee, Wisconsin.

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Correspondence: Marcy Neuburg, MD, Medical College of Wisconsin and Froedtert Memorial Lutheran Hospital, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.

E-mail: mneuburg@mcw.edu

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in areas such as duration, amount, and type of immunosuppression, type of transplant; age at transplantation; history of skin cancer before transplant; and use of single-center versus multicenter registry data. Therefore, looking at various studies over time, rather than one particular study, helps define the problem of skin cancer in transplant recipients. One of the first large studies on this subject was reported from New Zealand and Australia in 1993, more than 20 years after Penn's initial report. Sheil et al.⁴ used registry data and examined all de novo cancers in 6596 renal transplant recipients dating back to the 1960s. They found 1293 skin cancers, representing an incidence of 20%. Most patients (70%) had squamous cell carcinoma (SCC), 52% had basal cell carcinoma (BCC), and 3% had melanoma. They described skin cancers occurring along a continuum, from transplantation with progressive increases, so that by 24 years posttransplant, 66% of the patients had developed a cutaneous malignancy. Finally, this group reported that the SCCs in the study population were often multiple (69%) and prone to metastasis (7%). The mortality rate from SCC (in patients with SCC) was 5%. In 1996, Bavinck et al.⁵ used life-table analysis to measure the risk for skin cancer in 1098 renal transplant recipients in Queensland, Australia. Their conclusions were similar to the findings of Sheil's group in that they reported a 7% incidence of skin cancer in the first year posttransplant, increasing to 70% at 20 years posttransplant (Figure 1).

Although the problem of transplant-associated skin cancer was first detailed in renal transplant recipients, the advent of improved immunosuppressive techniques led to prolonged survival in heart transplant recipients. Several groups noted that the increased incidence of skin cancer was associated with higher doses of immunosuppressives used for successful heart transplantation. Ong et al.⁶ confirmed the previously noted reversal of the normal SCC:BCC ratio and reported a skin cancer incidence of 31% at 5 years and 43% at 10 years posttransplant. Additionally, they noted an increase in skin cancer-related deaths, with skin



Figure 1 Multiple squamous cell carcinomas in renal transplant patient.

cancer accounting for 27% of deaths occurring after the fourth year posttransplant. This same group performed a retrospective analysis of these latter patients and concluded that aggressive skin cancers are a major source of morbidity and mortality in the cardiothoracic transplant group.⁷

Fortina et al.⁸ studied skin cancer rates in 252 heart transplant recipients and compared them with skin cancer rates in 228 renal transplant patients in a single center. Like the Australian group, these authors reported an increased skin cancer incidence of 16% after 5 years and 33% after 10 years in the heart transplant group compared with incidences of 6% and 17%, respectively, in the kidney transplant group. However, multivariate analysis attributed the increases to increasing age at transplantation and not organ type or type of immunosuppression. In addition, they found that skin type II and increased sun exposure conferred a relative risk of 3 and 2.8, respectively, making these significant risk factors for the development of skin cancer after organ transplantation. These factors also likely explain the comparably elevated rates of skin cancer in the Australian transplant populations, because the unique genetics intrinsic to and the latitude of that continent confer an increased susceptibility to skin cancer.

Ramsay et al.⁹ performed a single-center, cross-sectional, longitudinal study in the United Kingdom in which 150 renal transplant recipients were followed up longitudinally and found to have a new skin cancer rate of 6.5% per year, increasing to 8.6% at 5 years and 10.5% after 10 years posttransplant. In 2000, Penn¹⁰ summarized the Cincinnati Tumor Registry data through 1998 relating to 11,483 tumors that developed in 10,787 patients. Of these, skin cancers were the most common, representing 38% of all reported malignancies, and 6% of skin cancers resulted in metastases to lymph nodes. Of these, 73% were SCCs and 17% were melanomas, and 5% of the patients died of skin cancer (60% SCC, 30% melanoma, 8% Merkel cell carcinoma).

The problem of metastatic SCC in organ-transplant recipients was further elucidated by Martinez et al.,¹¹ who retrospectively studied the characteristics of 68 organ transplant recipients with 73 metastatic skin cancers, noting a poor prognosis with a 3-year disease-specific survival of 56% in patients with metastatic SCC. More recent studies continue to document the magnitude of the skin cancer problem in solid

organ–transplant recipients. Using Medicare data in the United States, Kasiske et al.¹² reported a 20-fold increase in the incidence of nonmelanoma skin cancer (NMSC) in organ transplant recipients compared with the general population. Moloney et al.¹³ reported that NMSC in renal transplant recipients accounted for 1% of all NMSCs reported in Ireland, with the risk for invasive SCC being increased 82-fold in the group that underwent transplantation. Euvrard et al.¹⁴ in France looked at subsequent skin cancers after an initial SCC in kidney and heart transplant patients. At the 5-year follow-up of 188 patients at a single center, 100% of heart transplant patients and 88% of renal transplant patients developed a subsequent SCC.

In summary, increasing patient survival after solid organ transplantation is associated with the emergence of alarmingly high rates of skin cancer, especially NMSC. As the number of patients living with functioning grafts increases to greater than 150,000 (Figure 2),¹⁵ the overall burden of morbidity and mortality associated with skin cancer will only increase.

Immunosuppression: A Cause of Skin Cancer

Long-term immunosuppression of solid organ transplantation is clearly associated with an increasing incidence of skin cancer. What is less clear is whether the different drug regimens used over the past 40 years differ in their associated rates of skin cancer formation. Before asking whether reducing immunosuppression reduces skin cancer risk, the data on skin cancer and its relationship to the various immunosuppressive agents should be understood. Table 1 presents a general timeline of antirejection agents used in organ transplantation.

Over the past several decades, antirejection strategies have been specifically designed to target increasingly selective elements of the immune response mechanism. Early transplant physicians used a combination of glucocorticoids and total-body irradiation for immunosuppression, and typically recipients did not live long enough to evaluate the long-term effects of these treatments. Most modern antirejection regimens continue to include small doses of corticosteroids in levels that are not considered immunosuppressive. Little is reported in the literature regarding the role of steroids in skin cancer development in transplant patients. In 1987, Kelly et al.¹⁶ evaluated the effects of 4

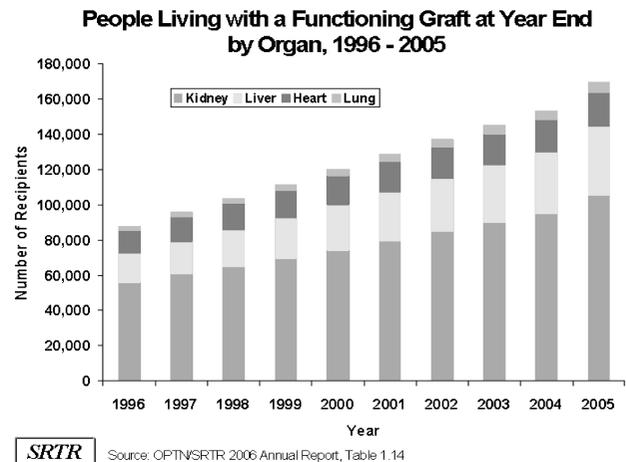


Figure 2 People living with a functioning graft at year end by organ, 1994–2003.

different immunosuppressants (azathioprine, prednisolone, cyclophosphamide, and cyclosporine) on ultraviolet-induced skin cancer using a hairless mouse model. They reported strong tumor-promoting effects with azathioprine (AZA) and cyclophosphamide characterized by a shorter induction latent period and a greater overall number of individual tumors. Prednisolone had no effect and cyclosporine (CsA) caused a mild reduction in the latent period. They concluded that the increased SCCs observed in renal transplant recipients treated with the combination of prednisolone and AZA was caused by the promotion of the carcinogenic effects of sunlight by AZA.

Much later, a Danish study performed by Sorensen et al.¹⁷ used a national prescription drug database covering the period 1989 through 1996 and examined 59,043 patients who were treated with long-term corticosteroids. All organ transplant patients were excluded. These investigators found an overall increase in NMSC risk in patients undergoing long-term corticosteroid regimens not related to organ transplantation. The standardized incidence ratio for SCC was 2.45 in this population, much lower than the observed rates in long-term transplant recipients described previously. A similar conclusion was reached in a population-based case-control study by Karagas et al.,¹⁸ who found a significant increase in SCC (adjusted odds ratio, 2.31) in patients treated with long-term (> 1 month) systemic corticosteroids for nontransplant indications.

The notion that some antirejection regimens may be more carcinogenic than others evolved in the late 1980s. Shuttleworth et al.¹⁹ compared the prevalence

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Table 1 Historical Timeline and Mechanism of Action of Common Antirejection Medications

Year	Agent	Mechanism of Action	Other Names
1959	Cyclophosphamide	Alkylating agent, disrupts DNA synthesis	Cytoxan
1962	6-Mercaptopurine	Purine analog, acts as antimetabolite decreased WBC production	Azathioprine Imuran
1983	CsA	Calcineurin inhibits production of class II MHC antigens; inhibits production of IL-2 by T-helper cells, thus blocking T cell activation and proliferation	Neoral Sandimmune Gengraf CsA or CyA
1994	Tacrolimus	Macrolide antibiotic, also a calcineurin inhibitor with similar mechanism as CsA	Prograf FK506
1995	Mycophenolate mofetil	Selectively inhibits T- and B-cell proliferation by blocking guanosine production required for DNA synthesis, antimetabolite	CellCept MMF
1999	Sirolimus	mTOR inhibitor, blocks cytokine signal transduction	Rapamune Rapamycin

Abbreviations: CsA, cyclosporin A; CyA, cyclosporine; IL, interleukin; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; mTOR, molecular target of rapamycin; WBC, white blood cell.

of dysplastic cutaneous lesions in 68 renal transplant recipients treated with CsA with that of 33 patients on AZA, and found a prevalence of 22% in the CsA group and 9% in the AZA group. This seemed to contradict the predictions of the study by Kelly et al.¹⁶ In 1994, Kehinde et al.²⁰ compared the incidence of de novo cancer in patients treated with prednisone, CsA, and AZA versus prednisone and CsA or AZA in a retrospective study of 492 renal transplant recipients. The triple-therapy group had a de novo cancer incidence of 17.5% compared with 4.5% in the other groups. These investigators concluded that the addition of AZA to maintenance regimens of CsA plus prednisone might predispose patients to a higher risk for developing cancer. Glover et al.²¹ compared renal transplant patients receiving CsA, AZA, and prednisolone with those receiving AZA and prednisolone, and found that patients on the triple-drug regimen developed more and earlier skin cancers compared with the group treated with AZA and prednisolone alone. The investigators concluded that the addition of CsA posed a threefold risk in the development of NMSC, especially SCC. This supports an earlier report by Sheil et al.⁴ that CsA is associated with an increase in skin cancer but not other malignancies.

Bouwes Bavinck et al.⁵ points out that studies comparing the influence of AZA to CsA on skin cancer are weakened by the fact that these studies must rely on historical controls. His group found no signif-

icant differences in the risk for developing skin cancer among patients treated with CsA alone or in combination with AZA and/or prednisone. Similarly, Hiesse et al.²² compared historical controls treated with AZA plus steroids with patients undergoing multidrug CsA-based immunosuppressive regimens. Although the groups did not differ in overall de novo cancer development, the CsA group developed more skin cancers (43% vs. 27%). However, the groups differed significantly in that the patients in the CsA group were significantly older at transplantation, a known risk factor for developing skin cancer.

In 1998, Dantal et al.²³ published a landmark study comparing low- and high-dose CsA regimens in 231 renal transplant recipients. Most patients were also taking AZA and prednisone. They found that halving the trough CsA serum level did not adversely affect graft or patient survival during the 6 years of the study. Furthermore, the reported de novo cancer rates were significantly lower in the low-dose group. Of these cancers, 66% were skin cancers; 26 in the high-dose group and 17 in the low-dose group, which was also a statistically significant difference. This study was the first to report that reduction of immunosuppression levels influences the rate of skin cancer development. These findings were supported by a study from Norway published in 1999 by Jensen et al.,²⁴ who performed a single-center cohort study on 2561 heart and kidney transplant patients. Like Shuttleworth et al.,¹⁹

Glover et al.,²¹ and Hiesse et al.,²² the Jensen group found that renal transplant patients treated with CsA in addition to AZA and prednisolone had a higher rate of SCC (but not BCC) than patients treated with AZA and prednisolone without CsA. The heart transplant recipients had an overall higher rate (threefold) of skin cancer compared with the kidney transplant patients, attributable to the higher levels of immunosuppression required by the cardiac patients. Jensen's conclusion that SCC development is related to the "therapeutic immunosuppressive load" is entirely consistent with Dantal's findings.

The study by Fortina et al.⁸ comparing posttransplant SCC incidence in heart and kidney recipients showed similar results. These investigators cited overall duration/amount of immunosuppression rather than the specific immunosuppressive regimen as a primary determinant of SCC development in transplant recipients, along with skin type, age at transplantation, and sun exposure. Ramsay et al.⁹ reached the same conclusions in their study of NMSC in renal transplant recipients.

From the late 1980s to 2000, a gradual change in thinking occurred regarding the manner in which immunosuppressive agents contribute to skin cancer formation. Although initial studies implicated specific agents (AZA, CsA), later studies showed conclusively that overall levels of immunosuppression rather than specific antirejection regimens were associated with increased rates of NMSC formation. But this story was not finished. In 1999, the U.S. Food and Drug Administration approved the mTOR (molecular target of rapamycin) inhibitor sirolimus for solid organ transplant recipients. mTOR inhibitors exhibit both immunosuppressive and antiproliferative actions through inhibition of signal transduction required for cell cycle progression, cell growth, and proliferation, and also have antiangiogenesis properties. The potential anticancer properties of this class of drugs were recently reviewed.²⁵

The initial reports touted the clinical advantages of relative CsA-sparing effect offered by sirolimus,²⁶ without specific mention of NMSC. Shortly thereafter, Mathew et al.²⁷ summarized the findings of 5 different phase II and III trials from 5 multicenter studies in which patients were treated with varying combinations and doses of sirolimus, CsA, prednisolone, and AZA. Although the follow-up period was only 2 years post-transplant, the aggregate data from these multiple stud-

ies suggested that sirolimus-based regimens resulted in lower cancer incidence, including skin cancer, compared with immunotherapies, including CsA. Kahan et al.²⁸ examined cancer rates in 1008 kidney transplant patients treated with sirolimus and cyclosporine with or without prednisone over 5 years. These authors reported an NMSC rate of 2.1%, which was significantly lower than that observed with traditional CsA, AZA, and prednisolone regimens. Similar findings were published by Kauffman et al.²⁹ using multivariate analyses of 33,249 patients from the Organ Procurement and Transplant Network/United Network for Organ Sharing database. Over a follow-up period of approximately 3 years, the de novo cancer rates in the patients treated with mTOR inhibitors (sirolimus or everolimus) were significantly lower than those observed in patients treated with calcineurin inhibitors (CsA or tacrolimus).

Two recent papers raise different issues that may further explain these observations. Tiu et al.³⁰ used global gene-profiling techniques to evaluate short-term CsA effect on a laboratory SCC cell line. They found that CsA affected a variety of genes involved in functions other than immunosuppression, including cell-cycle regulation, apoptosis, and oncogene/tumor-suppressor activation. They concluded that CsA was likely involved in the pathogenesis of SCC at the molecular level. The second study, by Khariwala et al.,³¹ was a dose-efficacy study using a murine model of intradermal tumors and pulmonary metastases using a murine SCC line. They compared the effect of the mTOR inhibitor everolimus given in 2 different doses with that of CsA or no treatment in mice that had been injected with SCC-VII to establish intradermal or pulmonary metastases. The animals treated with everolimus showed statistically significant tumor inhibition at both dosages tested compared with the CsA and no-treatment groups. The inhibition was seen in the animals with intradermal tumors and those with pulmonary metastases. These studies suggest that the observed differences in NMSC rates described with the use of mTOR inhibitors compared with CsA are likely multifactorial.

In summary, long-term immunosuppression is associated with an escalating incidence of NMSC in solid organ transplant recipients. Higher doses of calcineurin inhibitors seem to result in more NMSC. Reducing or replacing calcineurin inhibitors with mTOR inhibitors seems to result in lower rates of de

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novo malignancies, but longer-term studies are needed to confirm this observation.

Reduction of Immunosuppression

The role of reducing immunosuppression in the management of NMSC in solid organ transplant recipients can be viewed from 2 different, but equally important, perspectives. The first is NMSC prevention; that is, will minimizing immunosuppressive levels lead to reduced morbidity and mortality from skin cancer? The second is that of salvage in patients with advanced, aggressive, life-threatening skin cancers; specifically, does reduction of immunosuppression play a therapeutic role in the management of patients with a life-threatening SCC?

In terms of preventing NMSC, the data clearly support the notion that less immunosuppression results in lower rates of cancer. However, no large controlled studies specifically address this issue. Much of the discussion pertaining to reduction or cessation of immunosuppression is found in the liver transplant literature. What began as sporadic reports of noncompliant liver transplant recipients self-withdrawing their immunosuppressives has evolved into actual scheduled weaning of stable patients.^{32,33} But this is weaning with the goal of cessation, not as a strategy to prevent skin cancer. Weaning or cessation has also been used successfully to treat virus-associated tumors (e.g., Kaposi sarcoma, posttransplant lymphoproliferative disorder),³⁴⁻³⁶ but the success of these strategies is somewhat organ-specific in that long-term liver recipients tend to tolerate withdrawal with often-minimal morbidity. But again, this type of reduction is not being used as a preventive strategy. There have been anecdotal reports of transplant recipients with a history of multiple non-life-threatening NMSCs who experienced allograft failure in whom immunosuppression was subsequently stopped. In a report on 6 such patients from 4 centers, Otley et al.³⁷ noted deceleration of cutaneous carcinogenesis in 4.

Aside from anecdotal evidence, indirect evidence shows that reducing immunosuppression favorably impacts SCC development in the posttransplant period. In 2004, a single-center, prospective study from Italy³⁸ looked at the incidence of SCC and BCC in 230 heart transplant patients who were treated with varying doses of different immunosuppressive drugs. Patients were followed up for 3 years and a weighted linear

combination of the immunosuppressive agents (AZA, CsA, and prednisone) was calculated and found to be independently associated with an increased risk for developing SCC (but not BCC). The authors concluded that the risk for SCC is related to the level of overall immunosuppression rather than a particular drug, and recommend that patients at risk for SCC “should maintain as low as possible the level of immunosuppression.”³⁸ Although the study did not test the effect of immunosuppression reduction on subsequent SCC formation, it did suggest that more drug causes more cancer, and therefore less drug could be assumed to cause less cancer.

The best evidence for the role of reduced immunosuppression as a preventative strategy for NMSC comes from a recent study published by Euvrard et al.¹⁴ The goal of this study was to compare the individual rates of subsequent SCCs after the first SCC in a cohort of 188 kidney and heart transplant recipients. The patients studied were undergoing heterogeneous immunosuppressive regimens that included AZA, corticosteroids, CsA, mycophenolate mofetil, and tacrolimus. A secondary end point of the study was to explore the effect of immunosuppression reduction on new tumor formation. Half of the patients had at least one of their immunosuppressants reduced by at least 20% within the first year after they developed SCC. This resulted in 24 different immunosuppressive regimens and, as a consequence, each group had relatively small patient numbers and the patients differed in time since transplant, duration of follow-up, and type of transplant. Neither the specific immunosuppressive regimen nor the degree of immunosuppressive minimization was found to be statistically significant in terms of preventing subsequent SCCs. However, the investigators observed a significant reduction in new SCCs at the fifth year of follow-up in patients who had undergone immunosuppressive reduction (mean, 0.52 vs. 1.34; $P = .01$). These findings support a potential role for immunosuppression reduction in SCC prevention. The data also suggest that any future attempt to define the role of immunosuppression reduction in preventing SCCs might require follow-up of 5 or more years.

Multiple review articles describe much indirect evidence suggesting the efficacy of immunosuppression reduction/minimization for the management of multiple SCCs in transplant patients.³⁹⁻⁴¹ These papers all reach the same basic conclusion: because

reasonably good data show that SCC incidence is related to level of immunosuppression (rather than a specific immunosuppressive agent), one can infer that lowering the level of immunosuppression will result in fewer SCCs. Despite the lack of controlled trials showing the efficacy of SCC prevention through reducing immunosuppression, the literature refers to this as an accepted practice. In 2002, the European best practice guidelines from the Expert Group on Renal Transplantation advocated reduction of immunosuppression as a secondary preventative measure for SCC in transplant recipients. In recipients with multiple or recurrent SCCs, they recommend “further reduction of immunosuppression whenever possible.”⁴²

Returning to the initial question, whether minimizing immunosuppressive levels leads to reduced morbidity and mortality from skin cancer, the simplified answer is that multiple lines of indirect evidence suggest it does. A randomized, prospective, long-term follow-up is needed of patients with similar immunosuppressive regimens who have undergone dose minimization in response to SCC development compared with patients who remained on maintenance-dose therapy. Unfortunately, this is unlikely to occur in the foreseeable future. As multiple studies have shown, the problem of SCC in transplant recipients is one of long-term immunosuppression. Patients undergoing transplantation today are on different immunosuppressive regimens from those 5 years ago, who, in turn, are on different regimens from those 10 years ago. In the setting of a 5- to 10-year lag time for the development of SCC, meaningful studies with significant numbers of comparable patients are unlikely. With the addition of mTOR inhibitors, which are associated with inhibition of SCC in a murine model,³¹ the lines of evidence are likely to be further obscured.

The last area to be addressed is the role of immunosuppression reduction as a salvage strategy in patients with life-threatening SCCs. The data on this topic are extremely limited. No prospective randomized studies explicitly address this issue; only one retrospective, single-center study exists. Moloney et al.⁴³ identified 9 patients with what they termed *aggressive* SCC. These patients had SCCs that were deeply invasive (subcutis or muscle) and/or metastatic to regional nodes or local soft tissues. Through a medical records review, they found that 5 of the patients experienced no change in their immunosuppressive regimen after their diagnosis. Despite aggressive surgical

therapy, they developed metastatic SCC, all with functioning allografts. Four patients with aggressive SCC had their immunosuppression either stopped or significantly reduced. Of these, 1 died of metastatic SCC (with functioning graft) 16 months after CsA was discontinued. One patient was alive at 13 months without SCC recurrence or rejection after AZA was stopped and CsA was changed to tacrolimus. A third patient was alive and free of SCC with a functioning graft at 27 months after AZA was stopped. The final patient had both CsA and AZA stopped, and 24 months later was placed on dialysis with no recurrence of the cancer. Analysis of the data showed significantly improved outcomes ($P = .023$) in the group who underwent immunosuppression reduction or cessation. Despite its small sample size and retrospective design, this study is important because it is the first one showing that reduction or withdrawal of immunosuppression may prolong disease-free survival in renal transplant recipients with aggressive SCC. Notably, most patients who were offered withdrawal of immunosuppression declined, preferring the risk for metastases or death to the potential graft loss and resumption of dialysis. This observation is critical and must be incorporated into any discussion of patient care recommendations involving significant risk for irreversible loss of graft function.

The other study that directly addresses the issue of immunosuppression reduction in patients with life-threatening SCC was performed by members of the Reduction of Immunosuppression Task Force of the International Transplant Skin Cancer Collaborative and The Skin Care in Organ Transplant Patients Europe.⁴⁴ This group convened a panel of 8 dermatologists and 2 transplant physicians expert in the care of transplant patients with skin cancer. Thirteen clinical scenarios of escalating severity were presented, along with quality of life and anticipated mortality data (where available), to the panel members who were asked to assign 1 of 4 levels of immunosuppressive reduction (none, mild, moderate, or severe) to each scenario for each of 3 types of allografts (kidney, heart, liver). The first 7 scenarios represented increasing numbers of low-risk skin cancers associated with decreasing quality of life issues. Scenarios 6 through 13 presented individual high-risk tumors with escalating mortality statistics. The results of this study, which were by nature very subjective, showed that the expert panelists tended to accept escalating risk for

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rejection caused by aggressive immunosuppression reduction with increasing mortality statistics associated with life-threatening SCCs. In general, the panel recommended that mild reduction in immunosuppression was warranted for patients who developed fewer than 25 non-life-threatening SCCs per year. Moderate dose reductions and concomitant risk for allograft dysfunction were believed to be acceptable in patients with more than 25 SCCs or single cancers with a 10% 3-year risk for mortality. Severe reductions in immunosuppression were believed to be acceptable for skin cancer scenarios associated with a high probability of death. In general, this acceptance of risk was highly influenced by allograft type because the panelists were more willing to accept the risk of aggressive dose reduction and associated potential allograft failure in kidney patients than in heart or liver patients. Although this study lacks actual data showing the role of immunosuppression reduction in the management of transplant-associated skin cancer, it shows that experts consider this a viable strategy in the care of these often challenging patients.

Conclusions

Improvements in care of solid organ recipients have led to a greatly prolonged allograft and patient survival. Long-term survival requires continuous potent systemic immunosuppression, which is associated with a high incidence of cutaneous SCC. Numerous studies suggest that the risk for developing SCC is multifactorial, but that the overall level of immunosuppression, rather than the individual agent, is a major determinant of SCC incidence. The data supporting this relationship indirectly suggest that minimizing or reducing immunosuppression will result in fewer skin cancers. Despite the absence of confirmation by controlled trials, the concept that reducing immunosuppression will reduce skin cancer incidence in individual patients has become dogma within the transplant literature. The evidence that immunosuppression reduction or withdrawal plays a role in the treatment of aggressive SCCs is scant and somewhat anecdotal. Nonetheless, general consensus exists among experts that high-risk transplant-associated skin cancers warrant consideration of immunosuppression reduction or withdrawal as an adjuvant treatment strategy, particularly in situations where the allograft is not life-saving (e.g., renal). Lastly, the new class of antirejection

agents, mTOR inhibitors, shows promise in terms of antineoplastic properties and dosage-sparing of more traditional agents (calcineurin inhibitors and antimetabolites). Multiple studies have shown a lower incidence of malignancies, including solid tumors of all types,^{25–29,31} when mTOR inhibitors are used alone or in combination with standard agents. As these agents become more widely used, a concomitant plateau or possible reduction in the prevalence of transplant-associated SCC may occur.

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