Maintenance Versus Reduction of Immunosuppression in Renal Transplant Recipients With Aggressive Squamous Cell Carcinoma

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BACKGROUND. **There has been a significant increase in skin cancers in transplant patients in recent years. Transplant recipients are also more likely to develop skin cancers that are locally invasive with the potential to metastasize early.**

OBJECTIVES. **This study aimed to determine the effect of significantly reducing or stopping immunosuppressive therapy on prognosis of aggressive squamous cell carcinomas (SCC) in renal transplant recipients (RTRs).**

PATIENTS/METHODS. **Retrospective study of nine patients with aggressive SCC identified two groups, one whose immunosuppressive therapy was not altered and the other who had their therapy stopped or significantly reduced.**

RESULTS. **Aggressive SCC all occurred on the head and neck, with five of the primary tumors originating from the ear. Using a Wilcoxon-Breslow test to compare equality of survivor functions, reducing or stopping immunosuppression was associated with the prolongation of metastatic disease-free survival period ($p = 0.023$).**

CONCLUSIONS. **This nonrandomized pilot study suggests that reduction of immunosuppression in RTRs with aggressive SCC may improve prognosis compared to patients whose immunosuppression is unchanged. Allograft function may continue despite significant reduction of immunosuppression.**

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IMPROVED SURVIVAL of renal transplant recipients with consequent longer duration on immunosuppressive agents has increased the incidence of long-term transplant complications.[1] Renal transplant recipients (RTRs) develop neoplasms more commonly than the general population especially squamous cell and basal cell carcinomas of the skin.[2] Squamous cell carcinoma (SCC) in RTRs often displays an aggressive natural history with local invasion, early recurrence following treatment, higher rates of metastases, and increased morbidity and mortality.[3] A review of Irish RTRs between 1990 and 1993 showed an increased risk of skin cancers that were multiple and aggressive but no associated deaths.[4] In the past 5 years, however, there have been multiple recorded deaths from metastatic SCC in Irish RTRs. The increased number of deaths associated with such tumors in our center mirrors similar experiences worldwide.

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This retrospective study compared the prognosis in two groups of patients with aggressive SCC, one group that had significant modification or cessation of immunosuppression versus the other group that had no change in therapy. The outcome variable was the time to distant metastases.

Patients and Methods

Patients were defined as having aggressive SCC in the following settings.

1. Patients with SCC found to be deeply invasive to subcutis or muscle.
2. Patients with regional metastatic SCC at diagnosis. This included metastases in adjacent soft tissues or draining nodes.

Nine patients were identified with tumors that fulfilled the criteria of aggressive SCC. All attended Beaumont hospital, the national renal transplant center in Ireland, between 1994 and 2000. Data on patient demographics, previous skin cancers, duration

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of immunosuppression, treatment, and outcome were obtained from medical records. One pathologist (E.W.K.) reviewed the histology of each case recording tumor diameter, depth of invasion, differentiation, and involvement of surrounding structures.

Statistical analysis, using Fisher exact and Wilcoxon rank sum methods, evaluated patient demographics. Kaplan-Meier survivor functions and a Wilcoxon-Breslow test were used to estimate and compare metastatic disease outcome. Results were deemed significant for $p < 0.05$. The statistical software Stata (Version 8, Stata Corporation, College Station, TX) was used to analyze the data.

Results

The patient's demographics along with their management and outcome are presented in Table 1. Eight patients were receiving triple immunosuppression of cyclosporine, azathioprine, and prednisolone whereas one received a living related donor kidney and received azathioprine only. All patients were male with skin type I or II. The mean duration between date of transplant and development of aggressive SCC was 162 months (range 48–324 months). All tumors were located on the head and neck with five of nine patients' primary tumor occurring on the ear. The primary management of all tumors involved wide local excision. Lymph node dissection revealed involvement of draining nodes in three cases. In addition, five patients received radiotherapy postoperatively.

Two groups of patients were identified. Patients 1 through 5 received no change in immunosuppressive therapy. Patients 6 through 9 had immunosuppressive therapy stopped or significantly reduced on diagnosis of an aggressive SCC (Table 1).

Results of demographic differences between the two groups show no significant difference at the 5% level on the basis of initial treatment, lymph node involvement, age at transplant, or tumor size. Prior skin cancers, duration on immunosuppression, lymph node dissections, parotid metastases, and numbers who smoked were all increased in the group of patients who had no reduction in immunosuppression. Allowing for the small patient number, again significance was not detected at the 5% level. (Table 2)

Metastatic SCC was documented in patients 1 through 6 at a mean duration of 9 months (range 5–17 months) following the initial aggressive SCC (Table 1). These patients all died from their disease with functioning grafts. Patients 7 and 8 were alive with no recurrence or graft rejection at 13 and 27 months, respectively. Patient 9 had no recurrence and recommenced hemodialysis 24 months following cessation of immunosuppression.

The results show improved outcomes in reducing incidence of metastatic SCC for those whose immunosuppression was reduced or stopped. The follow-up is longer for those who had immunosuppression reduced as fewer patients in this group died from metastases ($p = 0.027$). A Wilcoxon-Breslow test shows significance at the 5% level (LR $\chi^2 = 5.14$, $p = 0.023$). Figure 1 illustrates Kaplan-Meier survivor estimates for the two groups, where improved outcomes for those with a reduction in immunosuppression are demonstrated.

Discussion

SCC most commonly occurs on sun-exposed sites and usually will not metastasize until well advanced.[5] Lesions occurring on the lip, the ear, and the external genitalia are more inclined to early invasion and metastases.[6] In the RTRs, however, all new lesions much be regarded suspiciously and biopsied as a matter of urgency to establish the treatment course of choice. SCC in RTRs can develop rapidly over weeks. These cancers have been alluded to in the past as "aggressive cutaneous malignancies" and "aggressive SCC" in the literature.[7,8] Histologic features associated with aggressive SCC include tumor thickness greater than 5 mm, poor differentiation, and invasion of underlying tissue.[7] Aggressive SCC has also been described in other immunosuppressed populations such as those infected with the human immunodeficiency virus.[9]

In some instances, an exponential growth phase of tumor development is entered with large numbers of new tumors emerging over a short period of time (patient 9 had developed 140 skin cancers over a 12-month period). In addition, tumors in transplant patients are more likely to display deeply invasive or metastatic behavior.[10] Recent studies indicate a relapse rate of 29% at 1 year and a 5 year survival of 25% with metastatic skin cancer in organ transplant recipients.[11]

Wide local excision with regional lymph node dissection is often required for aggressive SCC. Mohs micrographic surgery, where available, is recommended for high-risk tumors and for locally recurring tumors.[12] Patients with parotid node metastases generally fare better with combination surgery and adjuvant radiotherapy.[13] The treatment and follow-up of such patients involve a huge burden on surgical services and have a significant associated morbidity to the patient.

Previous studies have examined different immunosuppressive regimens and shown no differences in the incidence of nonmelanoma skin cancers.[14,15] Recent data suggest that newer immunosuppressive agents

Table 1. Patients with Aggressive SCC

Patient	*Number of NMSC Pre-Dx*	*Site of Aggressive SCC*	*Tumor Diameter (cm)*	*Depth Invasion*	*Differen-tiation*	*Local Spread*	*Treatment of Local Regional Disease*	*Lymph Nodes/ SCC-Positive*	*Change in IS Therapy at Dx*	*Duration From Dx to Metastases*	*Morbidity/Mortality*
1	12	Ear	2.5	Deep dermis	Poor	Parotid gland	WLE + ELND + RT	No	No change	5 months	Died at 7 months from metastatic disease.
2*	5	Ear	7	Subcutis	Poor	Salivary gland/perineural	WLE + ELND	No	No change	6 months	Died at 7 months from metastatic disease.
3	13	Orbit	5	Subcutis	Poor	Perineural	WLE + ELND	No	No change	6 months	Died at 11 months from metastatic disease.
4	25	Ear	1	Subcutis	Poor	Parotid/lymph nodes/muscle	WLE + TLND + RT	Yes	No change	9 months	Died at 10 months from metastatic disease.
5	25	Eyelid	1.2	Deep dermis	Poor	Lacrimal duct	WLE		No change	17 months	Died at 18 months from metastatic disease.
6	5	Eyelid	2.5	Subcutis	Well	Nil	WLE + RT		CyA stopped	10 months	Died at 16 months from metastatic disease.
7	1	Ear	3.5	Subcutis	Well	Parotid gland/ lymph nodes	WLE + TLND + RT	Yes	Aza stopped; CyA changed to tacrolimus		Alive with no recurrence or graft rejection at 13 months.
8	2	Ear	3	Subcutis	Poor	Parotid/lymph nodes/muscle	WLE + TLND + RT	Yes	Aza stopped		Alive with no recurrence or graft rejection at 27 months.
9	140	Temple	1.5	Subcutis	Poor	Muscle	WLE		CyA stopped; Aza stopped.		Back on dialysis from 24 months with no recurrence.

*Baseline immunosuppression of azathioprine only.
Abbreviations: Dx, diagnosis of aggressive squamous cell carcinoma; IS, immunosuppressive therapy; E/TLND, elective/therapeutic lymph node dissection; NMSC, nonmelanoma skin cancer; RT, radiotherapy; WLE, wide local excision.

Table 2. Patient Demographics

Variable	*No Change in Immunosuppression (Patients 1–5)*	*Withdrawal of Immunosuppression (Patients 6–9)*	*p Value*
Median age (years)*	48 (32–57)	47 (27–51)	0.539
Median number of skin cancers*	13 (5–25)	3.5 (1–140)	0.266
Median time from transplantation (months)*	224 (80–324)	91 (48–240)	0.221
Smoker (yes/no)	4/1	1/3	0.206
Median tumor diameter (cm)*	2.5 (1–7)	2.8 (1.5–3.5)	0.902
Mean tumor diameter (cm)†	3.34 (2.59)	2.62 (0.85)	0.617‡
Median follow-up from Dx to metastases or end of study (months)*	6 (5–18)	23(10–94)	0.027

*Numbers in parentheses are ranges.
†Number in parentheses is SD.
‡Student's *t*-test performed for comparison of tumor diameter means.
Abbreviation: Dx, diagnosis of aggressive squamous cell carcinoma.

might be less tumorgenic than standard immunosuppressive regimes. The potential advantage of reduced cancer risk for sirolimus and sirolimus derivatives has been proposed.[16]

Cessation of immunosuppressive medications for patients, in whom skin cancer developed after transplantation, resulted in deceleration of cutaneous carcinogenesis, decreased verrucae, and improved skin quality within 1 to 2 years.[17] We postulate that the degree of immunosuppression acts to switch a locally growing SCC into a tumor with metastatic potential. Reducing or stopping immunosuppression may allow a depressed immune system to recover and prevent tumor spread.

Withdrawal of immunosuppression in a transplant patient is an emotive issue. Most of the patients in this study declined this withdrawal, quoting risk of metastases and death as a preferable option to losing their graft and recommencing dialysis. There is, however, growing evidence that reducing immunosuppression may not result in graft rejection in the short term. It is standard practice in many institutions to reduce from triple immunosuppressive therapy to a cyclosporine-based double-drug combination after 3 months in renal allograft recipients with stable function.[18,19] Patient 9 (Table 1) retained his kidney for 24 months following cessation of all immunosuppression.

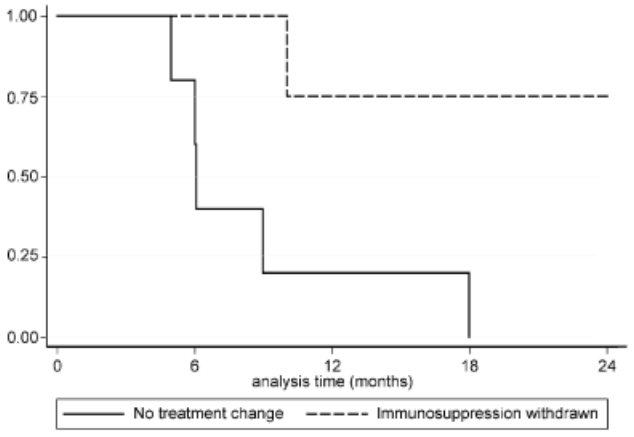

Figure 1. Kaplan-Meier estimates of time to metastases for immunosuppressive status.

Variables compared in Table 2, which may influence prognosis in aggressive SCC, do not attain significance at the 5% level. This is in part attributable to the low numbers present in both groups and consequently the power of the study to detect differences is somewhat compromised. In spite of the small patient sample for this particular study, however, a significant difference for those developing metastatic disease between the two groups was detected. Although larger randomized studies are required to confirm the findings of this study, a number of conclusions may be drawn. Early intervention and a high index of suspicion for recurrence and metastatic spread are required when dealing with skin malignancies in RTRs. There is a higher risk of aggressive behavior in tumors on sun-exposed sites in particular SCC of the lip and ear. Reducing or withdrawal of immunosuppression may prolong metastatic disease free survival in RTRs with aggressive SCC. Reduction of immunosuppression should be considered for transplant patients who develop substantial numbers of skin cancers. Prevention, in the form of patient education regarding sun avoidance and carefully designed skin screening programs, remains the cornerstone of management for all transplant patients.

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