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Reductions in immunosuppression after haematological or solid organ cancer diagnosis in kidney transplant recipients

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Summary

Few data exist on how immunosuppression is altered in kidney transplant recipients (KTR) following a diagnosis of cancer. This study investigated how immunosuppression was altered in KTR after cancer diagnosis and its effect on patient and graft survival. All KTR diagnosed with cancer at our centre from 1990 to 2012 were assessed. Drug regime and serum creatinine levels were recorded 1 year before, at time of, and 1 year after cancer diagnosis. Of 87 KTR who developed cancer (7.3% of transplanted population, $n = 1189$), 30 developed haematological malignancies and 57 developed solid organ cancers (SOC). In total, 38% of KTR presented with nodal or metastatic disease and 23 of 87 (26%) KTR died within 6 months of cancer diagnosis. Fifty-five KTR had records of pre- and postcancer diagnosis drug regimes. Thirty-six KTR had a (>50%) dose reduction or cessation of 1 or more immunosuppressive agents, and 19 no reduction in immunosuppression. In total, 2 of 36 (6%) of KTR who underwent a dose reduction suffered acute rejection that was reversed with methylprednisolone. Dose reduction/cessation of immunosuppression did not impair graft function, but also did not affect cancer free survival. Further larger prospective studies are needed to determine whether dose reduction alters relapse free cancer survival in KTR.

Introduction

Although kidney transplant recipients (KTR) have an increased rate of malignancy as compared to the general population [1], there are few data on how to manage immunosuppression and whether manipulation of drug regime has any effect on patient survival and/or kidney allograft outcomes. It is accepted that structured dose reduction can be curative for localized post-transplant lymphoproliferative disease (PTLD), but standardized chemotherapeutic options are more appropriate for advanced disease [2–5]. Although dose reductions are associated with fewer *de novo* malignancies in KTR [4–6], there are few data on whether such drug manipulations improve outcomes after malignancy and whether such changes adversely affect graft function. Therefore, we retrospectively audited the KTR in our centre, who were diagnosed with a malignancy after receiving their transplant, to assess the impact of any changes in immunosuppression on patient survival and graft function.

Patients and methods

The Australia and New Zealand Data and Transplant Registry was utilized to define KTR who developed cancer between 1990 and 2012 at our centre (Central and Northern Adelaide Renal and Transplant Service, CNARTS). Nonmelanoma skin cancers were excluded from the analysis. Drug regime, drug levels and creatinine at 1 year prediagnosis, at diagnosis of malignancy and at 1 year

postdiagnosis were recorded. Time from transplant to malignancy and survival postdiagnosis of both patient and graft was calculated. Changes in graft function were determined by comparing serum creatinine at 1 year postdiagnosis to that at time of diagnosis. Patients surviving less than 6 months postdiagnosis were not considered to have had a sustained period of dose reduction and were therefore excluded from all analyses comparing dose reduction and nondose reduction groups. In those patients who survived between 6 months and 1 year postdiagnosis, immunosuppression dose changes between diagnosis and 6 months postdiagnosis were recorded. Doses for each immunosuppressive agent were examined for each of the time intervals and a decrease determined by reduction in dose from time of diagnosis to 1 year post (or 6 months in those surviving between 6 months and 1 year). Categorical variables were tested with Fishers exact or chi-square tests. Differences between immunosuppressive drug doses between time points were tested with nonparametric Wilcoxon U-tests. Log-rank (Mantel–Cox) tests were utilized for testing the Kaplan–Meier survival curve analysis.

Results

Eighty-seven (7.3%) KTR out of a total cohort of 1189 KTR between 1990 and 2012 developed cancer; 30 haematological malignancies and 57 solid organ cancers. The solid organ cancers included: 16 renal tract, 13 gastrointestinal, eight lung, seven head and neck, seven prostate and six other (endometrial carcinoma, metastatic Merkel cell carcinoma, omental adenocarcinoma, rectal adenocarcinoma, thyroid adenocarcinoma, testicular seminoma). Staging records were available for 72% of SOC and 66% of haematological malignancies. Of SOC with staging records, 62.2% were localized and 37.8% advanced at diagnosis, where localized disease was considered confined to the primary organ and advanced disease was lymph node positive or distally metastatic. In total, 52.9% of haematological malignancies were localized and 47.1% advanced of those with staging records, where localized disease involved a single lymph node region (Stage 1) and advanced disease involved 2 or more lymph node regions, involved lymph node regions on both sides of the diaphragm or involved extralymphatic organs.

There was an even representation of haematological malignancies and solid organ cancers in the dose reduction group, but in the nondose reduction group there were far higher numbers of solid organ cancers (89%) versus haematological malignancies (11%). In addition, there was a much higher percentage of advanced disease at diagnosis in the dose reduction group (56%) as compared to the nondose reduction group (17%), for those with obtainable staging records (Table 1: patient demographics).

Table 1. Patient demographics.

	No dose reduction	Dose reduction
Numbers, *n*	19	36
Age at diagnosis, Median (Range)	54 (32–78)	61 (25–76)
Male gender, *n* (%)	12 (63)	26 (72)
Primary disease, *n* (%)		
IgA nephropathy	2 (11)	12 (33)
Glomerulonephritis	6 (32)	7 (19)
Polycystic kidney disease	2 (11)	5 (14)
Diabetes	1 (5)	2 (6)
Reflux	3 (16)	8 (22)
Other	5 (26)	2 (6)
Transplanted years to cancer diagnosis	9.2 (0.7–27)	8.6 (0.2–38)
Type of malignancy, *n* (%)		
Haematological	2 (11)	19 (53)
Solid organ cancer	17 (89)	17 (47)
Invasive/Metastatic/Diffuse*	2/12 (17)	14/25 (56)

*With obtainable records.

For the cohort as a whole ($n = 87$), median (range) age at transplantation was 49 (13–69), median time to diagnosis 7.8 years (0.25–38) and median age at diagnosis 59 (25–82). Median survival postdiagnosis was 4.3 years for haematological malignancies and 2.3 years for SOC (3.5 years for all patients). Overall mortality in the group with haematological malignancies was 60% (18/30 patients), with 4 of 18 (22%) of deaths due to sepsis/infection, 1 due to withdrawal of renal replacement therapy (RRT) and 13 of 18 (72%) due to progression of the haematological malignancy. Similarly, overall mortality in the SOC group was 65% (37/57 patients), with 2 of 37 (5%) of deaths due to sepsis/infection, 2 due to withdrawal of RRT, 1 of unknown cause and 32 of 37 (85%) due to progression of the malignancy. In those patients who died from withdrawal of RRT, one returned to dialysis as a result of recurrence of malignancy in the graft, 1 had graft failure at 13 years post-transplant and one was diagnosed with malignancy within 1 year of transplant and died 1 month postdiagnosis.

When comparing the dose reduction and nondose reduction groups, gender, age at cancer diagnosis and transplanted years to diagnosis were similar. There were some small differences in the primary renal pathology between the two groups (Table 1). Immunosuppression regime at time of diagnosis in both groups was comparable (Table 2: immunosuppression regime at cancer diagnosis).

Twenty-three KTR (15 SOC, eight haematological malignancies) surviving <6 months postdiagnosis were excluded from analyses comparing dose reductions to no change in immunosuppression. Nine KTR (eight SOC, one haematological) where records of drug doses were unattainable were

Table 2. Immunosuppression regime at cancer diagnosis.

	No dose reduction	Dose reduction
Numbers, *n*	19	36
Immunosuppression regimen, *n* (%)		
Azathioprine	9 (47)	18 (50)
Cyclosporine	8 (42)	20 (55)
Tacrolimus	4 (21)	7 (19)
Prednisolone	8 (42)	20 (55)
Mycophenolate	5 (26)	15 (42)
mTORi	0 (0)	5 (14)
Immunosuppression dose (mg), median (range)		
Azathioprine	100 (50–125)	100 (0–150)
Cyclosporine	150 (100–200)	188 (50–400)
Tacrolimus	2 (1–8)	3 (1.5–6)
Prednisolone	10 (5–10)	5 (0–25)
Mycophenolate	1500 (750–2000)	1000 (0–3000)
mTORi	0 (0)	0 (0–2)

mTORi, mammalian target of rapamycin inhibitors.

also removed from these analyses. Of the remaining 55 KTR, 36 underwent immunosuppression dose reductions and 19 had no reduction in immunosuppression. Azathioprine, cyclosporine and tacrolimus all showed statistically significant dose reductions (>50% reduction in median daily total dose) after cancer diagnosis without a significant change in serum creatinine (Table 3: dose changes following cancer diagnosis). Prednisolone showed a significant dose increase over this period, and mycophenolate, sirolimus and everolimus (mammalian target of rapamycin inhibitors, mTORi) did not show statistically significant changes (Table 3). Of the 36 dose reduction patients, 26 ceased 1 or more immunosuppressive agents.

There were two patients in the dose reduction group who experienced an episode of acute rejection, both of which responded to methylprednisolone treatment. Comparison of the Kaplan–Meier survival curves in the dose reduction and nondose reduction groups showed no significant difference in median survival of grafts ($P = 0.31$). Serum creatinine in the dose reduction group showed no increase over the period from diagnosis to follow-up at 1 year.

Table 3. Dose changes following cancer diagnosis.

	Prediagnosis dose (mg), median (range)	Postdiagnosis dose (mg), median (range)	*P* value
Azathioprine	100 (0–150)	0 (0–100)	0.001
Cyclosporine	188 (50–400)	0 (0–150)	<0.001
Tacrolimus	3 (1.5–6)	1.5 (0–4)	0.045
Prednisolone	**5 (0–25)**	**10 (0–10)**	0.018
Mycophenolate	1000 (0–3000)	1000 (0–2000)	0.247
mTORi	0 (0–2)	1.5 (0–2)	0.118

mTORi, mammalian target of rapamycin inhibitor.
Significant increase in prednisolone dosing indicated in bold.

Table 4. Outcomes.

	No dose reduction	Dose reduction
Numbers, *n*	19	36
Deaths, *n* (%)	10 (53)	18 (50)
Death by malignancy, *n* (%)	8 (42)	13 (36)
Median years from diagnosis to death	5.7	2.9
Recurrent cancer, *n* (%)	2 (11)	3 (8)
Cancer remission, *n* (%)	8 (42)	18 (50)
Creatinine levels, median (range)		
1 year precancer diagnosis	142 (74–228)	106 (80–194)
At cancer diagnosis	116 (70–378)	113 (64–349)
1 year postcancer diagnosis	135 (56–313)	109 (73–210)
Graft failure, *n* (%)	2 (19)	4 (11)

In 87 KTR with malignancy, there were 10 graft failures: one secondary to malignancy requiring nephrectomy, one recurrent IgA nephropathy, one diabetic nephropathy, two pre-existing chronic allograft nephropathy and one chronic vascular rejection. Four had no cause for the graft failure described. There was no increase in the rate of graft failure in those with a dose reduction as compared to those without dose reduction (Table 4: Outcomes). The graft failures in the dose reduction group ($n = 4$) were due to diabetic nephropathy, recurrent IgA nephropathy and 2 of unknown cause; however, the latter two grafts had lasted 17.4 and 23.0 years before failing.

In those with PTLD, the majority (19/21, 90%) were dose reduced and 4 died. Both cases where dose reduction was not performed died as a result of malignancy. In those with SOC ($n = 34$, with 17 patients undergoing dose reduction and 17 no dose reduction), there was, in fact, a significantly decreased survival in the dose reduction group ($P = 0.038$).

Importantly, chi-square and Fisher's exact test comparing disease state (localized and advanced) with dose modification (no dose reduction and dose reduction) in the SOC group gave a P value of 0.047, showing that those with advanced disease were more likely to have undergone a dose reduction.

Discussion

Despite KTR being followed up at least every 3 months, one-third to a half of KTR diagnosed with malignancy already had advanced disease at time of presentation. This suggests that malignancy in KTR is more rapidly progressive than in the general population, most likely due to their immunosuppressive burden.

Azathioprine, cyclosporine and tacrolimus all had statistically significant dose reductions upon diagnosis of malignancy with a low (6%) risk of acute rejection, which was

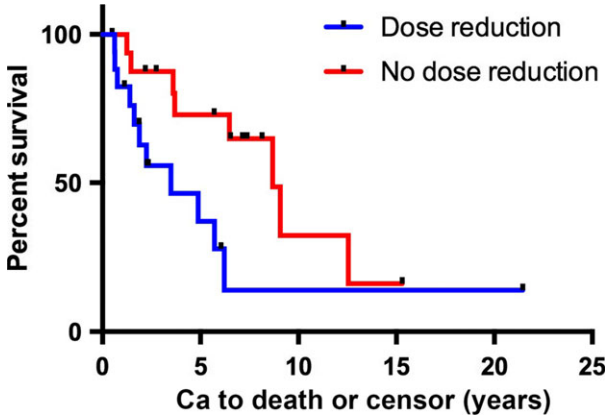

Figure 1 Survival of patients with solid organ cancer. Kaplan–Meier curve of 34 KTR who were diagnosed with solid organ cancer between 1990 and 2012: 17 KTR who had reduction and/or cessation of one or more drugs (dose reduction) and 17 KTR who had no alterations to immunosuppression (no dose reduction). There is a difference in median patient survival time of 3.5 years in the dose reduction group versus 8.7 years in the no dose reduction group. There is a significant difference in patient survival between groups ($P = 0.038$), with those undergoing dose reduction having shorter survival.

reversible with pulse steroid. Indeed, there was a corresponding increased in prednisolone doses in patients who had reductions in other immunosuppressive agents. Some patients ceased one or even more immunosuppressive agents without acute rejection or evidence of impact on graft function (see 1 year graft function, Table 1). This poses the question of whether patients could have been maintained on much lower doses of immunosuppression prior to the diagnosis of cancer.

The two most significant differences between the dose reduction and nondose reduction groups were a higher proportion of haematological malignancy patients in the dose reduction group (53%) versus nondose reduction group (11%) and the significantly higher proportion of patients with more advanced disease in the dose reduction group (56%) versus nondose reduction group (17%). This suggests that clinicians are more inclined to initiate substantial dose reductions in those patients diagnosed with a haematological malignancy, in keeping with the literature, and that they are more likely to initiate dose reductions in patients with more advanced disease, possibly to allow them the best chance of survival.

In the SOC group, dose reduction did not improve patient survival outcome (Fig. 1), showing dose reduction as secondary prevention of cancer may not be effective. However, given that patients undergoing dose reduction were statistically more likely to have more advanced disease, this could possibly explain the lack of effect of dose reduction on patient survival. We accept, however, that there are limitations as our cohort is relatively small and heterogeneous, and future studies are required.

A randomized controlled trial may be needed to definitely establish whether or not dose reductions in immunosuppression improves cancer survival/remission in KTR and to further define the amount by which a clinician can safely reduce immunosuppression doses. It may be that secondary prevention of cancer progression is not possible with dose reduction and that focussing on primary prevention and screening programmes is required.

Authorship

CMH: participated in data analysis, interpretation, writing and editing the paper. AJK: participated in data acquisition, data analysis, interpretation, writing and editing the paper. AB: participated in data acquisition. RPC: participated in research design, data interpretation and editing the paper.

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