Campath induction is associated with equalization of short term outcomes in renal retransplantation (but long-term outcomes are worse)

Andrew Kostiuk¹, Emre Eren¹, Graham Mitro¹, Michael Rees² and Jorge Ortiz³

¹College of Medicine and Health Sciences, University of Toledo, Toledo, OH, USA
²Departments of Urology and Pathology, University of Toledo College of Medicine and Health Sciences, Toledo, OH, USA
³Department of Surgery, University of Toledo College of Medicine and Health Sciences, Toledo, OH, USA

Abstract

Introduction: Few studies have evaluated the use of Alemtuzumab (Campath) induction in renal retransplantation (RRT).

Methods: We performed a retrospective analysis of 181 retransplants and 494 primary kidney transplants between 03/2004 and 05/2015. All patients were induced with Campath. We compared patient and graft outcomes.

Results: There was no significant difference in age, gender, or ethnicity. The percentage of recipients over the age of 65 (11.0% for retransplant vs 20.6% for primary, p=0.005) and mean PRA (20.1% for retransplant vs. 8.6% primary, p<.01) were significantly different. Donor KDPI was nearly identical (39.8 vs. 39.9, p>0.1). No significant differences were found in 1-, 3-, or 5- year patient survival (retransplant: 96.6%, 91.0%, 87.7% versus primary transplant: 95.8%, 89.1%, 81.9%, p>0.1). For death censored graft survival, only 3 and 5 year marks were significantly different (retransplant: 94.4%, 83.7%, 77.4% vs. primary transplant: 95.5%, 91.6%, 88.4%, p=0.008 and .002 for 3 and 5 years respectively). Graft rejection was measured at 1-, 3-, and 5- year periods (retransplant: 22.3%, 28.4%, 32.9% vs. primary transplant: 20.4%, 20.9%, 23.5%) with the only significant difference at 5 years (p<.05). Delayed graft function rates were not significant (7.8% vs. 10.4%, p>0.1). A combination of high PRA and retransplant status was associated with the highest risk of rejection (35.7%).

Conclusion: Despite high rejection rates overall, our results demonstrate acceptable short term outcomes with Campath as an induction agent for kidney retransplantation.

Introduction

Campath-1H (Alemtuzumab) is a humanized monoclonal antibody that targets the CD52 glycoprotein on lymphocytes and rapidly depletes T and B cells. Its use for renal transplantation began in 1998 [1,2]. It is now regularly employed as an off-label induction agent [3]. As part of a steroid-free or reduced steroid regimen, Campath can mitigate the negative side effects of steroid use on kidney transplants [4-6]. Campath induction may potentially expand the use of high-risk, extended-criteria donors and improve outcomes with African Americans, who traditionally fare significantly worse when receiving renal grafts [7,8].

Renal retransplantation (RRT) is a subgroup of recipients who generally experience inferior outcomes. 14.3% of the transplant waitlist is comprised of patients awaiting RRT and 11.5% of all kidney transplants from 2013 were retransplants [9]. RRT patients experience increased incidences of rejection and reduced graft survival compared to primary transplant [10,11]. This diminished success rate is correlated to both the time to retransplant after primary allograft failure and previous graft survival time [12,13]. Despite the increased risk associated with RRT, it has established itself as a superior option compared to remaining on dialysis [10,14,15].

Numerous reports have described encouraging recipient outcomes with Campath induction therapy in renal transplantation, but few report its efficacy in retransplantation [16]. In this manuscript, we compare the outcomes of retransplant and primary transplant patients who underwent induction therapy with Campath. We surmised that Campath would be efficacious, at least in the short term.

Materials and methods

We performed a retrospective analysis on a database of 181 retransplant patients and 494 primary kidney transplant patients induced with Campath at the University of Toledo Medical Center in Toledo, Ohio between March 2004 and May 2015. Donor and recipient information was requested from UNOS and all patient data was collected and analyzed retrospectively using Transchart electronic medical records software. This project was approved by the Institutional Review Board at the University of Toledo Medical Center (IRB 200640).

Donor information included type of donor (living or deceased), age, gender, ethnicity, cause of death, history of diabetes and hypertension, donor criteria (extended or standard), and KDPI.

Correspondence to: Andrew Kostiuk, 2510 W Village Dr. Toledo OH 43614, 330-323-9252, USA, E-mail: Drew.Kostiuk@rockets.utoledo.edu

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Recipients’ information included: age, gender, ethnicity, delayed graft function, history of diabetes and hypertension, graft rejection, date of rejection, and 1-, 3-, and 5-year graft (death censored) and patient survival rates (Figure 1).

All patients received an immunosuppression induction regimen of methylprednisolone 500 mg intravenously (IV) (Solu-Medrol, Pfizer, New York, NY) and Campath (Alemtuzumab 30 mg IV [or .5 mg/kg if less than 60 kg]).

Postoperative steroid taper consisted of: methylprednisone 250 mg IV post-operative day (POD) 1, methylprednisolone 125 mg IV POD 2, prednisone 60 mg PO POD 3, prednisone 40 mg PO POD 4, and prednisone 20 mg PO POD 5.

Tacrolimus 1.5 mg (Prograf, Astellas Pharma, Tokyo, Japan) PO BID and mycophenolate sodium (Myfortic Novartis Pharmaceuticals, Basel, Switzerland or Cellcept, Genentech, San Francisco, CA) 540 mg PO BID were both started POD 1. Tacrolimus levels were measured and titrated to the correct dose. Side effects permitting, mycophenolate sodium was increased to 720 mg PO at discharge. Steroids were generally tapered to off by one month.

Antimicrobial prophylaxis was started post-operatively with sulfamethoxazole (800 mg)-trimethoprim (160 mg) 1 tab PO (Bactrim DS, AR Scientific, Philadelphia, PA) 3 times per week and clotrimazole troche 10 mg dissolved in the mouth 4 times per day following oral care. valgancyclovir 450 mg PO (Valcyte, Hoffman-La Roche, Basel, Switzerland) was prescribed based on established risk factors.

Statistical analysis was performed using SPSS 21.0 (IBM, Armonk, New York). Continuous variables assessed with t-tests or Mann-Whitney U when appropriate. Categorical variables assessed using Pearson’s Chi-square test. Survival analysis was performed using the log rank method. P-values of less than 0.05 were considered significant.

**Results**

**Pre-campath era**

598 patients from 1996—2004 (179 RRT and 447 primary transplant, or PTX) were included as part of pre-Campath data. Within this section, patient survival for RRT was 96.6%, 94.9%, and 87.7% for 1-, 3-, 5-year intervals compared to 94.4%, 91.9%, and 80.8% for PTX. Death censored graft survival for RRT was 90.5%, 84.9%, and 75.4% (1-, 3-, 5-years) vs. 95.3%, 93.9%, and 88.1% for PTX. Mean PRA was 17.2 for RRT vs. 12.3 for PTX (Figure 2).

**Campath study donor and recipient characteristics**

A total of 675 patients underwent kidney transplantation with Campath induction. 181 were retransplant (RRT) and 494 primary transplant (PTX). Mean recipient age was 51.2 years for RRT and 52.6 years for PTX. Significantly fewer RRT patients were >65 years of age compared to PTX (11.0 vs 20.6%, p=0.005). RRT and PTX populations were 59.7% (108 patients) and 65% (321 patients) male. Notable differences in racial characteristics of recipients included percentage of Hispanic patients (5.9% of RRT vs 1.1% of PTX p=.006) and white patients (80.1% RRT vs 67.6% PTX, p=0.002). An increased mean PRA (20.1% vs. 8.6%, p=0) and PRA>20% (31.1 vs 14.1%, p<0.001) was seen in the RRT group. CMV+ was similar (61.3% vs 58.0%) (Table 1). KDPI of donors was comparable (39.8 RTX vs 39.9 PTX). The number of deceased donor kidneys and extended criteria donors (ECD) were similar (p=0.429 and 0.158). Of the reasons for transplant, only diabetes mellitus was significantly different. (p<0.05) (Table 2 and Figure 3).

**Patient survival**

Patient survival at 1, 3, and 5 years for RRT was 96.7%, 91.2%, and 87.9% respectively compared to 95.8%, 89.3%, and 83.3% for PTX (Table 3) with no statistically significant difference (p=0.639, 0.505, and 0.215). Cox survival analysis indicated RRT was non-significantly protective in univariate analysis (HR 0.60, CI 0.376-0.971, p>0.05) and not relevant to the final model (Table 4). All causes of patient death studied were similar. (Table 5).

**Graft survival and delayed graft function**

1-, 3-, and 5-year death censored graft survival rates were 94.4%, 83.7%, and 77.4% for RRT versus 95.5%, 91.6%, and 88.4% for PTX (p=0.67, 0.008, and 0.002) (Table 6). RRT status was a risk for graft loss on univariate analysis (HR 1.63, CI 1.987-2.454, p=0.018) but the effect did not remain in the final model (HR 1.49, CI 0.881-2.379, p=0.144)
Retransplantation remains the most effective treatment of end stage renal disease for those who have experienced the loss of an initial graft [11,17,18]. The percentage of retransplants performed has increased to 15% in 2016 [19]. Patient survival among recipients for initial and second transplants has become comparable over the years [11,20]. Our analysis yielded no significant difference between RRT and PTX patient survival in 1-, 3-, or 5-year intervals (Table 3). Final multivariate analysis for patient survival did not note being African American as a significant risk factor (as has been commonly reported) but did designate high KDPI, older age at transplant, and Hispanic race as significant risk factors (Table 4) [21,22].

Past RRT evaluations have noted the markedly worse outcomes in retransplant graft survival in comparison to what one might expect in primary transplants [10,20,23-25]. Recently, Khalil et al. found that RRT graft survival approached PTX 1-, 3-, 5-, and 10-year graft survival, but were still significantly inferior [11]. Our 1-, 3-, and 5-year death censored graft survival rates in RRT (94.4%, 83.7%, 77.4%) and PTX (95.5%, 91.6%, 88.4%) groups were significantly different in

Table 7. Multivariate model for death-censored graft survival.

<table>
<thead>
<tr>
<th>Factor</th>
<th>RRT</th>
<th>PTX</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retransplant</td>
<td>1.551</td>
<td>0.954</td>
<td>0.076</td>
</tr>
<tr>
<td>Rejection History</td>
<td>3.878</td>
<td>2.402</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>KDPI</td>
<td>1.02</td>
<td>1.011</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>PRA&gt;20%</td>
<td>2.174</td>
<td>1.31</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Table 8. Cause of graft failure.

<table>
<thead>
<tr>
<th>Factor</th>
<th>RRT</th>
<th>PTX</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Rejection</td>
<td>13.0%</td>
<td>15.8%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Chronic Rejection</td>
<td>22.2%</td>
<td>7.5%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Allograft Complication</td>
<td>11.1%</td>
<td>3.3%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Death</td>
<td>24.1%</td>
<td>54.2%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Recurrent Disease</td>
<td>3.7%</td>
<td>5.8%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Primary Non-Function</td>
<td>1.9%</td>
<td>5.0%</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Other</td>
<td>24.1%</td>
<td>8.3%</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>

(Tables 7). Delayed graft function (DGF) was comparable at 7.8% vs. 10.4%, p>0.1)

Cause of graft failure

Significant differences in causes of graft failure between RRT and PTX respectively were chronic rejection (22.2% vs 7.5%, p<.05), allograft complication (11.1% vs 3.3%, p<.05) and death (24.1% vs 54.2%, p<.05) (Table 8). Acute rejection, recurrent disease, and primary nonfunction were similar. (p>0.05) (Table 8).

Discussion

Retransplantation remains the most effective treatment of end stage renal disease for those who have experienced the loss of an initial graft [11,17,18]. The percentage of retransplants performed has increased to 15% in 2016 [19]. Patient survival among recipients for initial and second transplants has become comparable over the years [11,20]. Our analysis yielded no significant difference between RRT and PTX patient survival in 1-, 3-, or 5-year intervals (Table 3). Final multivariate analysis for patient survival did not note being African American as a significant risk factor (as has been commonly reported) but did designate high KDPI, older age at transplant, and Hispanic race as significant risk factors (Table 4) [21,22].

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only the 3 and 5 year categories (p=.008 and .002 respectively). On multivariate analysis, we found rejection history, and PRA >20% as the most significant risk factors for inferior graft outcomes (Table 7). Being that there is no significant difference between graft survival over a 1 year period, we believe this lends credence to the notion that Campath will be efficacious in narrowing the disparities between RTX and PTX in the short term.

When examining causes of graft failure, death and chronic rejection were the most common in RRT and death was most prominent in the PTX group. Other publications examining RRT have cited rejection, surgical complications, chronic allograft nephropathy, chronic glomerulonephritis, and hypertensive nephropathy as common causes of graft failure [10,21,26,27].

While we discovered chronic rejection to be significantly more common in RRT versus PTX (p<.05), no significant difference existed in overall acute rejection. This conforms with the findings of Dunn et al. but differs from Heaphy et. al., who demonstrated that retransplant recipients were more likely to be treated for acute rejection [13,28]. Our data shows no significant difference in rejection based upon 1, 3, and 5 year intervals (RRT: 22.7%, 30.9%, 34.7% vs PTX: 20.9%, 24.4%, 26.7%, p=.654, .163, .115 respectively). Ingsathit et al., reported rejection rates of 16.6% while Ahmed et. al noted that patients receiving a second transplant had rejection rates of 8% [10,23]. Similar values were reported elsewhere, indicating our rejection rates are higher than what is typically reported [29-31]. We attributed this increased rejection to the steroid free regimens and low dose MMF. Therefore, we have modified our protocols to induce how dose MMF sooner in the two, but did not list individual values [10,23].

Due to the relative risk of rejection that both high PRA and RRT status impose, we also evaluated what combination of these factors posed the greatest overall threat [13,28]. Unsurprisingly, the combination of high PRA and retransplant history presented with the highest combined possibility of graft rejection (35.7%) when compared to RRT and low PRA, PTX and high PRA, and PTX and low PRA. Therefore, we recommend maintenance steroids and very close follow-up of these high-risk patients.

The incidence of DGF following a deceased donor kidney transplant are estimated to range between 23 and 50 percent with higher levels reported in RRT compared to PTX [13,18,33,34]. We did not observe a significant difference in DGF between RRT and PTX in our investigation (10.4% vs. 7.8% p=.376). Additionally, the number of our patients experiencing DGF is 10-15% lower in both categories than other studies examining retransplantation [20,35]. This implies Campath may be more effective than non-depilating antibody agents in mitigating unknown donor and transplant center characteristics that contribute to DGF [33-35]. This might also reflect utilization of higher quality organs in patients transplanted at our center. Mean KDPI for RRT group was 39.8% and not significantly different from PTX. The utilization of high KDPI (>75) was 16.9% for RRT and 12.7% for PTX (p=.238). While mean KDPI is a commonly reported statistic, frequency of high KDPI (>75) is not often disclosed in the literature. Prevalence of ECD kidneys was 15.3% for RRT and 10.3% for PTX (p=.158). Louvar et al. reported ECD kidneys comprising a similar proportion of their donors [35]. Further, over 70% of our patients in both cohorts received deceased donor kidneys (Table 2).

Before the introduction of Campath at our facility, patient survival for RRT was 96.6%, 94.9%, and 87.7% for 1-, 3-, 5- year intervals compared to 94.4%, 91.9%, and 80.8% for PTX. Death censored graft survival for RRT was 90.5%, 84.9%, and 75.4% (1-, 3-, 5- years) vs. 95.3%, 93.9%, and 88.1% for PTX. This represents acceptable RRT results predating the addition of Campath, which ideally reflects a sound protocol. However, the pre-Campath outcomes were not evaluated in this investigation as the data and demographic collections were not part of our updated database and would have suffered from significant error effects.

Our analysis possesses numerous strengths. The relatively large sample size, single-center focus, long-term follow-up, and a consistent protocol eliminate uncertainty caused by hidden variables. Furthermore, ours is the only examination to focus solely on the utilization of Campath as an induction agent in renal retransplantation.

There are some limitations to our study as well. The retrospective nature allows for confounding variables that may affect the strength of our results. Additionally, because we performed a single center analysis, results may not apply to all centers. We were limited in analysis by relatively small proportions of certain ethnic groups. No other induction methodology was used as a control group. Finally, inconsistencies in data collection limited our pre-Campath comparison.

**Conclusion**

The uses of Campath as an induction therapy for primary renal transplant have been well documented and produced positive findings [16]. We believe that its use extends to retransplant procedures as we have found acceptable outcomes within that population. There is no significant difference in patient survival between RRT and PTX reflecting the recent trend [11,20]. Though there were some significant differences in graft survival rates, Campath was shown to be effective in equalizing graft survival in the short term. The overall short term equalization eventually “wears off” and the negative outcomes begin to present in at risk populations like RRT patients. Additionally, although rejection levels in this study were higher than what might be found elsewhere, this is largely resulting from the steroid free protocol administered to patients and has no reflection on the efficacy of Campath to generate positive outcomes as continued steroid maintenance resulted in a subsequent decline in rejection rates. Therefore, we advise steroids and close follow up in high risk recipients even if they are out a long time. Based on all the findings in this project, we encourage routine usage of Campath versus other induction agents in retransplant patients as it can help shield this population from the inherent risk of rejection that they possess. However, these patients need close observation in the long term as outcomes are significantly inferior. If an institution is unable to provide the long term surveillance required, other induction therapies should be considered.

**Contributions:** Kostiuk, A.: Wrote the paper; Eren, E.: Wrote the paper; Mitro, G.: Statistical analysis and wrote the paper; Rees, M.: reviewed the paper; Ortiz, J.: designed the study, reviewed and edited the paper.
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References

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