Cancer-Free Survival Following Alemtuzumab Induction in Heart Transplantation

S. Chivukula[a], M.A. Shullo[b], R.L. Kormos[c], C.A. Bermudez[c], D.M. McNamara[c], and J.J. Teuteberg[c,*]

[a]School of Medicine, University of Pittsburgh School of Medicine; and [b]Department of Pharmacy and Therapeutics and [c]Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

ABSTRACT

Background. The malignancy rate after alemtuzumab (C-1H) induction in cardiac transplantation is unknown.

Methods. A retrospective analysis from a single center for all patients that underwent cardiac transplantation from January 2000 to January 2011 and that had no history of malignancy before transplantation was performed. Patients induced with alemtuzumab were compared with a group of patients receiving thymoglobulin or no induction and assessed for 4-year cancer-free post–heart transplantation survival.

Results. Of 402 patients included, 185 (46.0%) received alemtuzumab, 56 (13.9%) thymoglobulin, and 161 (40.0%) no induction. Baseline characteristics did not differ between groups: mean age 54.0 years, male 77.1%, white 88.6%, ischemic cardiomyopathy 49.0%. The calcineurin inhibitor was tacrolimus in 98.9% of alemtuzumab patients, 98.2% of thymoglobulin patients, and 87.0% of the noninduced ($P < .001$). The secondary agent was mycophenolate mofetil in all but 16 noninduced patients (9.9%), who received azathioprine. The 4-year cancer-free survival did not differ between groups: 88.1% alemtuzumab, 87.5% thymoglobulin, 88.2% noninduction; $P = .088$. The 4-year nonskin cancer–free survival was 96.8% for the alemtuzumab group, 96.4% for the thymoglobulin group, and 95.7% for the noninduced; $P = .899$.

Conclusions. Neither the 4-year cancer-free survival nor the 4-year nonskin cancer–free survival differed between the alemtuzumab, thymoglobulin, and noninduced groups.

SURVIVAL following cardiac transplantation has significantly improved over the past 2 decades, with national rates for graft survival now 91.6% at 6-months, 88.6% at 1 year, and 73.1% at 5 years [1–3]. However, the majority of this improvement has occurred in the first 6 months after transplantation, after which the rate of graft loss has not changed appreciably [1]. The leading causes of long-term graft loss after heart transplantation continue to be cardiac allograft vasculopathy and malignancy [4,5].

Approximately 50% of all patients who undergo cardiac transplantation are treated with induction therapy in addition to the standard calcineurin-based immunosuppressive regimen. Although induction therapy is associated with a lower risk of early acute cellular rejection, it is also associated with an increased risk of malignancy [1,6]. A study by Swinnen et al in 1990 demonstrated a nearly 10-fold increase in post-transplantation lymphoproliferative disorder (PTLD) among patients receiving the cytolytic agent muromonab-CD3 (OKT3) [7]. Several new induction agents have since been introduced, and various studies have analyzed their associated rates of malignancy; incidence rates of post-transplantation malignancy from 1% to 21% have been reported, depending on induction drug [6]. Some, such as recominant thymoglobulin, have been found not to influence the rate of malignancy in heart recipients but to shorten the time to its onset and to hasten the time to death following malignancy [8,9].

Presented in part at the American Transplant Congress Annual Meeting, Boston, Massachusetts, June 2012.

*Address correspondence to Jeffrey J. Teuteberg, MD, Heart and Vascular Institute, University of Pittsburgh Medical Center, Scaife Hall, Suite 556, 200 Lothrop Street, Pittsburgh, PA 15213. E-mail: teutebergjj@upmc.edu

360 Park Avenue South, New York, NY 10010-1710

0041-1345/14/$–see front matter
http://dx.doi.org/10.1016/j.transproceed.2014.04.001

Alemtuzumab, a humanized rat monoclonal antibody targeted against the CD52 antigen, a glycoprotein widely expressed on mononuclear cell surfaces, has been used as induction therapy in kidney, pancreas, intestine, liver, and lung transplantation [10–17]. The use of alemtuzumab induction after cardiac transplantation has demonstrated a superior freedom from rejection but no difference in survival at 1 year compared with patients who did not receive induction [4]. However, there are no data regarding its impact on the development of malignancies compared with other induction agents or with those who did not receive induction.

MATERIALS AND METHODS

Study Design and Patient Population

We performed a single-center retrospective review of all patients that underwent cardiac transplantation at the University of Pittsburgh Medical Center from January 1, 2000, to January 1, 2011. Patient demographics, immunosuppressive regimens, and clinical outcomes were obtained from the Transplant Patient Management System (TPMS), an institutional database that prospectively collects data on all patients undergoing thoracic transplantation. Patients that underwent retransplantation or multiorgan transplantation or that had malignancies before cardiac transplantation were excluded from the present analysis. Of 469 total heart transplant recipients identified during the specified time period, 12 were retransplants, 40 were multiorgan transplants, and 41 were in patients with preexisting malignancies. The remaining 402 unique heart transplant patients were included in the present analyses. All patients consented before having their data entered into the TPMS, and this study was approved by the University of Pittsburgh Institutional Review Board.

Immunosuppression and Clinical Management

Before January 1, 2006, only patients considered to be high-risk, typically because of renal insufficiency, received induction therapy, and all other patients were treated with a calcineurin inhibitor (CNI), a secondary agent, and steroids typically weaned over the first 6–12 months after transplantation. The goal tacrolimus levels were 10–12 ng/mL for those who received induction and 12–15 ng/mL for those who were not induced. The goal mycophenolate mofetil (MMF) dose was 1,500 mg twice daily. Since October 2006, all patients received routine induction therapy with alemtuzumab and were subsequently treated with a CNI and a secondary agent with no postoperative steroid use. Goal trough levels for tacrolimus were 8–10 ng/mL for those receiving alemtuzumab with a goal MMF dose of 750 mg twice daily. Surveillance biopsy protocol for rejection did not differ between patient groups.

Study Measures and Statistical Analyses

Comparisons between groups of patients receiving alemtuzumab induction, thymoglobulin induction, or no induction were made with the use of analysis of variance for continuous variables and chi-square or Fisher exact tests for categoric variables. Actuarial survival was performed and person-time incidence rates computed for patients grouped by induction agent. Cancer incidence rates were calculated for every 6 months until a maximum of 48 months after transplantation. These are reported per 1,000 person-months. Additionally, survival analyses were performed with the use of the Kaplan-Meier method, and comparisons were made with the use of a Cox proportional hazard model. A P value of $<.05$ was designated as statistically significant. All data were analyzed with the use of SPSS version 19.0 (Chicago, Illinois).

RESULTS

Demographics

Of 402 total heart transplant recipients in our study, 185 received alemtuzumab induction, 56 received thymoglobulin, the remaining 161 received no induction therapy. As presented in Table 1, these patient groups did not significantly differ in baseline characteristics (age, sex, ethnicity) with the notable exception that there was a higher prevalence of patients receiving alemtuzumab who had a history of tobacco use ($P = .003$). Ischemic cardiomyopathy was the most common indication for heart transplantation in all groups (49.0%) and more common among thymoglobulin-receiving patients ($P = .036$). Because of the routine implementation of alemtuzumab induction in October 2006, mean follow-up time varied between the 3 patient groups, ranging from 33 ± 20 months among those receiving thymoglobulin to 35 ± 15 months among those induced with alemtuzumab and 41 ± 15 months among those not induced ($P = .001$).

Immunosuppressive regimens across patient groups also are presented in Table 1. With the exception of 16 noninduced patients who received azathioprine, the secondary agent of choice in all patients was MMF. The CNI was tacrolimus in all but 24 patients, who received cyclosporine. Mean tacrolimus trough levels in 6-month intervals after transplantation are represented in Fig 1. The alemtuzumab group consistently had the lowest mean tacrolimus levels until 30 months after transplantation, after which there was no difference among the 3 groups.

Malignancies

The incidence and type of tumors in the 3 patient groups by induction agent are presented in Table 2. There were a total of 48 confirmed malignancies in 402 patients (11.9%) during follow-up. Skin cancers accounted for 30 (62.5%) of the 48 neoplasms. These were most commonly squamous cell, followed by basal cell carcinomas with three melanomas; notably, the 3 patient groups did not significantly differ in the rates of skin malignancies. Among nonskin cancers, the incidence of prostate adenocarcinomas was highest (5 of the 48 neoplasms, 10.4%), followed by lung adenocarcinomas (among all lung cancers). Again, the incidence of cancer was statistically similar among patient groups, although all of the lung tumors occurred in patients receiving alemtuzumab or thymoglobulin, none among those receiving no induction. Only 3 cases of PTLD were diagnosed in the follow-up period: 1 in a patient induced with alemtuzumab and 2 in noninduced patients, none in thymoglobulin recipients.

The incidence rates of any cancer per 1,000 person-months among all patients grouped by induction agent are presented in Table 3. Adjusted for survival time, at 4 years