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Long-Term Outcome With the Use of OKT3 Induction Therapy in Heart Transplant Patients: A Single-Center Experience

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ALTHOUGH posttransplant patient survival has improved in the last 3 decades, acute and chronic rejections are still major causes of death following transplantation. During the early 1980s, the success obtained with the use of OKT3 as therapy for allograft rejection motivated transplant centers to use it as prophylaxis for the rejection of solid allografts. During the following years, the use of OKT3 as induction therapy in heart transplantation became popular because its use was expected to reduce the incidence of rejection episodes and improve short- and long-term patient survival.

In the past 10 years, many heart transplant centers around the world have experimented with the use of OKT3 induction, and the results reported from those studies have varied.[1–5] A possible explanation for the lack of consistency in these results might be the differences in patient population, immunosuppressive protocols used by each center, and the control group used.

After 9 years of using OKT3 induction therapy in heart transplant patients performed at our center, we analyzed our data and we present our results.

METHODS

Between July 17, 1987, and July 28, 1996, 149 orthotopic heart transplants were performed at our center. Eight patients suffered immediate donor failure and were excluded from this analysis. Additionally, 27 cytomegalovirus (CMV) mismatched patients (donor CMV positive and recipient CMV negative) were excluded from this study. The remaining 114 patients were retrospectively assigned to one of two groups according to OKT3 induction therapy received. Patients in group I ($N = 85$) received OKT3 induction and patients in group II ($N = 29$) did not. Demographic data, rejection episodes, infections, cancer incidence, and patient mortality information was collected for all patients.

Immunosuppressive Therapy

All patients received cyclosporine, azathioprine, and steroids as maintenance immunosuppressive therapy after heart transplantation.

Rejection

Diagnosis of rejection was based on endomyocardial biopsy findings using the criteria of the International Society for Heart Transplantation. Early and severe rejection episodes were treated with solumedrol 500 mg a day for 3 consecutive days. Cases of refractory rejection were given OKT3 at a dose of 5 mg/d for 7 to 10 days. Chronic rejection episodes without hemodynamic compromise were treated with oral prednisone tapering from 100 mg/d.

Infections

Only those infection episodes that required hospitalization were included for this analysis.

Malignancy

Nonskin cancer cases were analyzed for these two groups.

Statistics

Results are expressed as mean values ± standard deviation (SD). Comparisons between the two study groups were performed using chi square and/or Fisher Exact Test for categorical data. Student's *t* test for paired two-sample for means was used to compare numerical data. Survival was generated by the Kaplan-Meier method. Statistical significance was defined as $P < .05$.

RESULTS

Eighty-five patients received OKT3 induction therapy (group I), while 29 patients did not (group II). Demographic information is shown in Table 1. Patients in group I were younger and had a significantly longer cold ischemic time ($P < .05$).

Short Term Results

Mean stay in the intensive care unit after transplantation was 7.4 ± 8.8 days for patients in group I versus 7.7 ± 7.0 days for patients in group II ($P > .05$). Mean posttransplantation hospital stay was 15.7 ± 10 days for patients induced with OKT3 versus 19.7 ± 17.9 days for patients not induced with OKT3 ($P > .05$).

The average posttransplant time for the first rejection episode was 69 versus 71 days in patients with and without OKT3 induction, respectively. First year rejection incidence

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Table 1. Demographic Information

	OKT3 Induction Group ($N = 85$)	Non-OKT3 Group ($N = 29$)	*P* Value
Age at transplant	50 ± 13	57 ± 7	<.05
Male	9% ($N = 67$)	69% ($N = 20$)	>.05
Female	21% ($N = 18$)	31% ($N = 9$)	
Percentage of reactive antibody (PRA)	0.3%	0%	>.05
Cold ischemic time	124 ± 51	103 ± 41	<.05
Tissue typing match	1.0 ± 0.9	1.2 ± 1.5	>.05
Caucasian	70% ($N = 60$)	90% ($N = 26$)	>.05
Other	30% ($N = 25$)	10% ($N = 3$)	
History of blood transfusion	29% ($N = 24$)	17% ($N = 5$)	>.05

was similar between the two groups (51% versus 45%). The number of rejection episodes was 1 ± 1.2 versus 0.7 ± 0.8 for patients in group I and II, respectively (Table 2).

The incidence of first year cytomegalovirus and bacterial infection between the two groups were 6% versus 5%, and 22% versus 23% respectively ($P > .05$).

Principle mortality reasons during the first year posttransplantation in group I were acute rejection (1%) and AGAS (1%), while in group II they were acute rejection (3.5%) and intracraneal bleeding (3.5%).

Long-term Results

Five-year nonskin cancer incidence was 9% versus 3% for patients with and without induction therapy, respectively ($P > .05$).

The long-term causes of mortality were AGAS (7%), cancer (6%), infection (5%), and acute rejection (1%) for patients in group I versus acute rejection (7%) and intracraneal bleeding (3.5%) for patients in group II. The differences in the short- and long-term causes of mortality were not statistically significant between the two groups ($P < .05$).

There was no significant difference in short and long-term patient survival between our two groups (Table 2).

DISCUSSION

The management of transplant patients is an ever evolving process. Heart transplantation is not an exception, and in the past 2 decades new and more potent immunosuppressive drugs have been used for prophylaxis and treatment of rejection episodes. Cyclosporine, OKT3, mycophenolate mofetyl, and tacrolimus are examples of such new medications.

Each year, heart transplant centers from around the world evaluate the safety and efficacy of different combinations of immunosuppressive agents with the objective of improving short- and long-term patient survival. However, the comparison of the results obtained by different centers is difficult and in many cases not possible. Population factors such as donor/recipient tissue typing homogeneity, overall health situation of donors and recipients, and the patient's medical insurance coverage and socioeconomic status play an important role in the success of heart transplantation. Also, center-specific factors regarding immunosuppressive therapy (type and dose), concomitant drug therapy (antibiotic, antiviral, antifungal prophylaxis, etc.), and management of long-term complications (hyperlipidemia, skin cancer, lymphomas, etc.) have a significant effect on graft and patient survival.

We know that prospective, randomized, multicenter studies are an excellent way to control the above mentioned variables; however, in the real world most centers deviate from strict protocols once the study is completed. For this reason, we believe that although it is of great importance to know the experience of other centers regarding the safety and efficacy of any given treatment, it is more important to

Table 2. Short- and Long-Term Posttransplant Patient Outcome

	Group I ($N = 43$) *OKT3 Induction*	Group II ($N = 29$) Non-OKT3 Induction	*P* Value
Follow-up time (y)	4.9 ± 2.6	2.9 ± 1.7	<.05
Posttransplant days for first rejection episode	69 ± 49	71 ± 84	>.05
First year rejection incidence	51% ($N = 43$)	45% ($N = 13$)	>.05
First year rejection episodes	1.0 ± 102	0.7 ± 0.8	>.05
First year CMV infection incidence	6%	5%	>.05
First year bacterial infection incidence	22%	23%	>.05
5-year nonskin cancer incidence	9%	3%	>.05
5-year lymphoma incidence	5%	0%	>.05
Patient survival			
1-year	98%	93%	>.05
3-year	75%	87%	
5-year	65%	73%	

evaluate the center's individual results some time after using a new drug therapy. Our results are consistent with the published reports of most heart transplant centers.[6] Carrier et al[6] in 1992 performed a review of worldwide studies published regarding OKT3 use in solid organ transplantation. They concluded that OKT3 induction therapy had not been proven to be effective in improving short- or long-term heart transplant survival.

CONCLUSIONS

In our study, OKT3 induction therapy failed to improve the incidence and total number of acute rejection episodes as compared to the non-OKT3 induction therapy. We also did not observe any beneficial effect in the short- or long-term patient survival. Due to these results, we do not consider it advantageous to continue using this agent for routine induction therapy in our heart transplant center.

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