Do Patients Who Participate in a Clinic Experimental Protocol Have the Same Probability of Success From That Who Were Not Selected or Refused To Participate? Outcome Surveillance, Safety, and Bioethical Considerations in Kidney Transplant Clinical Research

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ABSTRACT

Introduction. Safety in conducting a clinical trial is a prerequisite for patients who will be enrolled into that study. The aim of the present study was to evaluate retrospectively if patient and graft survival were similar among patients who participated in clinical trials versus those who did not.

Patients and Methods. We evaluated pretransplant and posttransplant characteristics of 245 kidney transplant (KT) patients who were selected to participate in at least one Phase II/Phase III clinical trial. We compared them with 361 KT patients who were not enrolled or refused to participate in those clinical trials; all studies were conducted at a single transplant center. Inclusion/exclusion criteria were as noted for each individual protocol. Only studies with enrollment at time of graft implant were considered.

Results. Selection of patients participating in clinical trials in general exclude high-risk patients. In our experience, only 36% of transplanted patients were selected for a multicenter, prospective, randomized, international study that included changes to the strategies in the administration of immunosuppressive drugs already on the market or development of a new immunosuppressant. After 5 years, graft and patient survival rates were similar between those who participated and those who did not participate in a clinical study. Although our data were collected retrospectively, an alternative design to achieve these conclusions would be a noninferiority study.

Conclusions. Our results demonstrated similar rates of graft and patient survival among enrolled patients versus nonenrolled patients. Outcome surveillance offers safety in participating in clinical trials that involve changes in standard immunosuppression therapy and are part of the research necessary to develop patient-centered medical interventions.

THE MODERN transplant era is based on immunosuppression (IS) advances that have led to drastic reductions in the incidence of acute rejection without affecting the incidence of chronic immune damage in any organ [1]. Current, potent new therapies explore novel biological mechanisms; although the goal is to achieve better results, the long-term risks of these therapies are unknown [2]. Safety in conducting a clinical trial is a prerequisite for those patients who will be enrolled into these studies.

The aim of the present study was to evaluate if patient and graft survival rates were different depending on whether the patient had participated in 1 of 13 international, multicenter, randomized, intervention clinical trials.

MATERIALS AND METHODS

From 1997 to 2013, our Kidney Transplant Program at Policlinico Gemelli (Università Cattolica del Sacro Cuore, Rome, Italy) performed 613 kidney transplants (KT). During this period, 245 KT

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0041-1345/14
http://dx.doi.org/10.1016/j.transproceed.2014.07.065

patients were selected and invited to participate in 1 of 13 multicenter, international, randomized, Phase II/Phase III clinical trials. All protocols were previously approved by local ethics committees for human experimentation, and all research procedures were in accordance with the Declaration of Helsinki [3]. Trials planned early intervention in IS therapy (at induction phase or early postoperative IS protocol). Inclusion/exclusion criteria were as noted for each individual protocol. Only clinical trials with enrollment at time of graft implant were considered. To make comparisons of death and patient outcomes (ie, survival at year 5 follow-up), we considered the remaining 361 KT patients who were not enrolled or refused to participate in those clinical trials, in the same transplant center, as the control group. Demographic data and clinical characteristics of the recipients and donors were retrospectively obtained from a prospective databank or directly reviewed from the patient chart (when necessary). At the time of study enrollment for each protocol and successive updates or specific procedures, informed consent was appropriately presented and signed, allowing patients to submit to any study intervention; patients could withdraw consent at any phase. Limitations of the present study include that it was retrospective and single center in design; multiple trials were analyzed as a group; and the mean follow-up was only 5 years.

RESULTS

Table 1 summarizes demographic and clinical characteristics before and after transplantation. Patients in clinical studies had a mean higher age; organs were always from deceased donors; and diabetes and dyslipidemia were more prevalent in patients enrolled in clinical studies. Cold ischemia time and positive findings for hepatitis C virus were lower in this group. No differences in biopsy-proven acute rejection were noted. Suspected acute rejection episodes (not biopsy-proven) were higher among control subjects (data not shown; incidence of 27% in this group vs 17% in clinical protocol patients [P = .006]). Estimated glomerular filtration rates at years 1 and 3 (the former, data not shown) were higher among clinical study patients at these time points but not at the end of year 5.

No statistical differences in graft or patient survival rates were reported. Causes of graft loss after 5 years for the clinical studies group and the control group, respectively, were as follows: death with a functioning kidney, 4.7% vs 7.9% [P = not significant (NS)]; nephroangiosclerosis, 1.3% vs 0.3% [P = NS]; medical/surgical, 1.7% vs 2.7%; acute rejection, 1.3% vs 1.6% [P = NS]; recurrence of primary disease, 0.9% vs 1.4% [P = NS]; primary nonfunction, 0.9% vs 2.7% [P = NS]; chronic rejection, 0.9% vs 4.1% [P = .021]; interstitial fibrosis/tubular atrophy without other specified cause, 0.4% vs 5.1% [P = .002]; and posttransplant glomerulopathies (except recurrences), 0.4% vs 1.6% [P = NS]. Causes of death at the year 5 follow-up were as follows for the clinical studies group versus the control group: infective, 1.7% vs 3.0% [P = NS]; neoplasia, 1.7% vs 1.1% [P = NS]; hepatologic/hematologic, 0.9% vs 1.6%; unknown, 0.9% vs

Table 1. Pretransplant and Posttransplant Characteristics Among Clinical Study Participants (n = 245) and Control Subjects (n = 368)

Characteristic	Clinical Study Group (n = 245)	Control Group (n = 368)	*P* Value
Pretransplant characteristics			
Age, y	**48 ± 13**	45 ± 11	**<.001**
Male sex	63%	62%	NS
Body mass index, kg/m^2	24 ± 3	24 ± 3	NS
Previous transplant	6.9%	4.1%	NS
Live related donor	0	**6.3%**	**<.001**
Immunologic primary disease	29.0%	23.1%	NS
Diabetes	12.1%	5.4%	**.003**
Hypertension	74.6%	70.2%	NS
Dyslipidemia	35.8%	12.2	**<.001**
HBV positive	0.9%	1.1%	NS
HCV positive	3.5%	11.1%	**.001**
Cold ischemia time	12 ± 4	13 ± 6	**.005**
Nonstandard deceased donor	39.1%	30.7%	**.040**
Posttransplant characteristics*			
Delayed graft function	25.8%	39.3%	**.001**
Primary non function	0.9%	2.7%	NS
Acute rejection, biopsy proven	16.4%	16.8%	NS
NODAT	2.6%	15.2%	**<.001**
Year 1 follow-up			
eGFR†	50 ± 23	46 ± 22	**.027**
Graft survival	93.5%	90.5%	NS
Patient survival	97.8%	97.8%	NS
Year 5 follow-up			
eGFR†	47 ± 32	43 ±25	NS
Graft survival	88.8%	84.8%	NS
Patient survival	94.8	95.4	NS

Abbreviations: eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; NODAT, new-onset diabetes after transplant; NS, not significant.

*Before postoperative day 90; considers wound infection, wound dehiscence, hematoma, and lymphoceles.

†Estimated by using the abbreviated Modification of Diet in Renal Disease formula.