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Discussion

Professor Lars-Erik Gelin (Gothenburg, Sweden): The transplant program in San Francisco has contributed a great deal to clinical transplantation. Today we have learned about donor-specific blood transfusions prior to HLA-nonidentical and to MLC-reactive related renal transplants, stressing improved and excellent graft function after three months and after 12 months. The price to pay, however, was a sensitization of about one-third of the intended transplant pairs.

Since 1977, we have required at least three blood transfusions to be given to the recipient six weeks before transplantation, without observing a sensitization in more than one patient, who underwent acute transfusions because of an intercurrent operation.

We have, however, given leukocyte pooled blood. That might be one explanation for the lack of sensitization. My first question to Dr. Salvatierra is: What kind of blood did you transfuse?

With the protocol, we have obtained (slide) a 95% graft survival among our HLA-nonidentical related renal transplants in contrast to the 70% graft survival rate at 12 months we had prior to this protocol.

(slide) The striking improvement in graft survival and function became evident in our retrospective study of primary cadaveric grafts before we introduced the compulsory pretransplantation program. The recipient who did not receive any blood transfusions before the grafting had a 30% lower graft survival rate at 12 months than the previously transfused recipients.

(slide) In our series, we have been able to identify two important factors which when combined result in a poor outcome of cadaveric grafting. These are two incompatibilities in the HLA B-locus in nontransfused recipients, as seen from this slide. When, however, only one incompatibility existed for HLA B-antigens in the previously transfused recipients, the graft survival was the same as for grafts without foreign antigens.

For these reasons, I do not believe the donor specificity in the transfusions is the important factor, and again I stress Dr. Salvatierra's hypothesis that induction of suppressor cells might well result from nonspecific blood transfusions.

I would like to hear Dr. Salvatierra's comments on the different kinds of blood used for pretreatment, and the time schedule before transplantation.

Dr. Nicholas A. Halasz (San Diego, California): It is fascinating for those of us who started out in transplantation ten or 12 years ago and initially used buffy-coat-poor blood and then switched to frozen blood when it became available in order to avoid all those evil antigens present in leukocytes, platelets and plasma to see ourselves turning around and using blood intentionally in recipients, initially nonspecifically. Now Dr. Salvatierra tells us that blood of

donor origin is even better. I think this is a remarkable report. These studies need to be continued and other series like this one undertaken. I have no doubt that this will happen, maybe even faster than it should.

I have a few questions I would like to bring up regarding the mechanism involved. I would love to see a specific sort of altered responsiveness to have been induced in the recipient, because it would represent truly the first time that clinically we have been able consistently to modify in a specific way the immunologic response of a recipient. Dr. Salvatierra has reported on a smaller series of pretransfused recipients before, at which point MLCs were repeated, using plasma after donor specific transfusion. I wonder if you would tell us whether you have done more of these and whether there has been any change in the MLC done in posttransfusion recipient plasma.

I do think, however, that we do not need to use specific immunologic modification as an explanation. If one looks at this simply numerically, and Dr. Salvatierra hinted at this, if one does a one haplotype matched transplant with high MLC responsiveness between donor and recipient, one gets about a 60% one year survival rate. Then, if one-third of the group is simply sorted out, presumably the same one-third that would have rejected transplants, one comes up with a survival rate of higher than 90%. Thus, by simple selection, one can explain just about everything that has happened. Along these lines it would be of interest whether you had done other immunologic surveillance tests such as DNCB skin testing, CML and so on, to see whether one is dealing with a high-responder group in those who became cross-match positive after transfusion. You certainly could be selecting a nonspecific low-responder group or a specific recipient group with low Iga or Igr responsiveness, or you could be selecting donors who provide a weak second signal.

Five or six years ago a fascinating study was done by Shackman at Hammersmith, Professor Welbourn's institution, where a number of one haplotype matched living related donor–recipient pairs were transplanted with skin from all the potential donors. These patients differed from Dr. Salvatierra's in having low dose immunosuppression with 50 mg azathioprine per day. That group came up again with a similar percentage; 61 or 62% of those patients had skin graft survival for six weeks or longer. These then underwent transplantation for six weeks or longer. These then underwent transplantation and had essentially a 100% kidney survival rate. Here again I believe selection was the process involved, and the circumstances are not entirely dissimilar.

Dr. Salvatierra, since you are recommending that patients with one haplotype mismatches who are high MLC-responders be transfused from their future donors, would you recommend to centers which do not have MLC typing available routine transfusion of all one haplotype matches prior to their being transplanted?

DR. G. MELVILLE WILLIAMS (Baltimore, Maryland): I commend Dr. Salvatierra and his group for a courageous study. Purposely to transfuse a recipient with blood from an individual who could offer a kidney with a 60% chance of a normal life at one year is something that concerned me. This course of action presumes an ability to distinguish sensitization on the basis of a positive crossmatch and to use as donors only individuals who had produced the desired "transfusion effect."

On looking at Dr. Salvatierra's slides, I am worried about some of the early rejection crises, particularly the one that occurred on the first day after transplantation. I can only interpret this early rejection as evidence of presensitization, for the normal primary immune response would take longer than one day.

Therefore, I wonder what Dr. Salvatierra, having done three transfusions, would think about doing four transfusions? Would he allow greater time for the immune response and perhaps select out another group of patients in this manner?

I am also interested in mechanisms that could confer some sort of tolerating action by blood transfusions and wonder if Dr. Salvatierra had repeated stimulation indexes or whether he has done additional *in vitro* assays such as CML's? Could he detect some weakening of the specific immune response?

DR. OSCAR SALVATIERRA, JR. (Closing discussion): As one can tell from our presentation and the presentations of the discussants, the story of donor-specific transfusions is not complete.

In reference to Professor Gelin's remarks, the patient population in this study was only the MLC-incompatible group that, in our hands, did not give better graft survival than if a cadaver kidney was used. Yes, there was sensitization to the blood donor in 30% of the patients, but on serial monitoring to the panel, a panel composed of 30 unrelated donors, the sensitization proved to be narrow, quite specific and directed to that blood donor, as might be expected from exposure to limited antigens from the use of a one haplotype matched blood donor. There was no evidence of significantly increased broad sensitization to the panel in those 15 recipients who had no third party transfusions before or during the time of the donor-specific transfusion process. In fact, in these patients, the greatest increase in broad, warm T-cell sensitization to the panel after the donor-specific transfusion, was 6% in one patient. More important, potentially unsuccessful living related transplants have been avoided in these MLC incompatible patients. For the potential donors, blood donation was harmless compared with donating a kidney, which could be rejected.

As far as the blood products used, we are using fresh packed cells or whole blood, with no difference in transplant outcomes. As far as rejection incidence with either whole blood or packed cells, there was no difference. In patients followed for three months, we have seen six rejection episodes in 13 patients receiving whole blood, three rejection episodes in seven receiving packed cells alone, and one in a group of three receiving a combination of whole blood and packed cells.

I appreciated Dr. Halasz's and Dr. Williams' remarks. In reference to a change in the MLC, particularly in the culture in recipient plasma, there was no significant change after transfusion or after transplantation. We have performed CML's on a number of patients, and in several of these there has been inhibition of CML, not after the transfusion, but well after transplantation.

In response to one of Dr. Halasz's questions, presently I think it is difficult to recommend donor-specific transfusions for all one-haplotype matches, but if our experience is confirmed by others, and if it continues to prove safe, of course, this is a definite consideration.

We are now only looking at small parts of a large puzzle. For the present, there will have to be continued speculation about the mechanisms involved in the donor-specific transfusion process, but they do pose some intriguing possibilities.

Certainly, before transplantation, selection is the principal process. After transplantation, when you consider that there was a relatively low incidence of rejection episodes, that they were mild in nature, that they were usually easily reversed, and that the general course of these recipients was somewhat similar to HLA-identical siblings, all this translates into some modification of host immune response. However, at this time there is no good scientific evidence for what type of host modification exists, yet the background for such modification exists in that the potential recipient has had repetitive challenge with modest dosages of the same donor-specific antigens that were to be present in the subsequently transplanted kidney.