Heart transplantation: Peri- and postoperative management

DR SUDHIR KUSHWAHA: Greetings. I'm Dr Sudhir Kushwaha, medical director of the Mayo Clinic heart-transplant and VAD program, and I'm joined today on Mayo Clinic Talks by my colleague Dr Rocky Daly, who's the surgical director of the heart-transplant and VAD program.

We will be discussing heart transplantation, and this is part 2 of a two-session podcast. Just to briefly summarize, in the first session, we discussed transplant candidacy and the difference between status 1A, status 1B, and status 2 patients once the patients have been listed. We discussed the role of bridge-to-transplant VAD therapy and the status that confers on the patient once they have had an implant and how that's changed the field.

We're going to move on now and talk further about a number of transplant-related areas including peri- and postoperative management, long-term management, and long-term mobility and mortality.

Let's start off with a patient who has been listed and who undergoes heart transplantation. I'm going to ask Rocky to discuss what the major operative issues are, including the process of harvesting the donor and the time from harvesting to implantation.

DR RICHARD DALY: Thanks, Sudhir. It's good to be back with you for the second session here. The process of transplant really starts when we get an organ offer, and UNOS [United Network for Organ Sharing] a few years back started an electronic system for organ offers that allows the coordinator, the donor coordinator with the local organ procurement organization who's at the hospital with the donor, to make offers in an electronic fashion and offer organs to several institutions at one time.

On the receiving end of the offers, we will get a number of offers where the other institutions are also being offered the donor simultaneously, and this speeds along the allocation process because every donor is not appropriate for every recipient. And, on the other hand, we will get offers that we would hope to use but find that we are down the list a little further from somebody who has already taken the heart. It causes rumors sometimes that a transplant might be occurring, and I just mention it so that if your patient brings up this sort of thing, it's related to the UNOS process of the electronic allocation.

We accept the organ if it's appropriate for our recipient. If it actually comes to us, they phone us and we review the details about the donor and make sure that we understand all the details and that things are appropriate. If we still agree that the donor looks appropriate for our recipient, we start the process. If our recipient's not in the hospital, we call them in and make arrangements for their admission in a very timely manner.

We make arrangements with the donor-procurement coordinator for our team to go and perform the procurement and do the final assessment. And once our team arrives at the hospital, they make sure that things are acceptable from the standpoint of consent and blood group, all the things that we need to double check, and they assess the heart itself—visibly—to be sure that it's acceptable.
If all is well, then we go ahead with the transplant. The heart is procured at the same time, along with the abdominal organs and the lungs and transferred back to our institution and we'll have made our timing arrangements so that we're ready for the heart when it arrives, and we've usually already started the operation in our recipient and go ahead with the transplant.

The major concern is a risk of primary graft failure, and there is a small risk of that even with today's levels of assessment of the donor and with the ways of preservation of the organs. But we still probably see a 2% or 3%, maybe 5%, incidence of unexplained primary graft failure that isn't really related necessarily to a rejection.

DR SUDHIR KUSHWAHA: What do we do as the initial immunosuppressive strategy in the operating room? You've sewn in the new heart. The patient is going to be reperfused shortly. What do we give initially to try to prevent acute rejection in the operating room?

DR RICHARD DALY: Our protocol is to give one dose of steroids before the patients go to the operating room, to give the steroids a few hours to have full activity, and then after we have come off cardiopulmonary bypass and have given protamine so bleeding isn't too much of an issue, we give another dose of high-dose steroids. We follow this in our protocol with [antithymocyte globulin] ATG, which we believe helps in terms of avoiding calcineurin inhibitors perioperatively, preserving renal function—we've found it very reliable in terms of eliminating risk of cell-mediated rejection perioperatively.

DR SUDHIR KUSHWAHA: I think most centers would give an initial dose anyway of what we would call induction therapy, usually ATG in this day and age, although previous agents have included daclizumab, or OKT3 is another agent that used to be used. But the use of these induction agents routinely postimplant is not so widespread now. I think we still use them—maybe up to a week or so after transplantation, but the use of them is somewhat variable, wouldn't you say, Rocky?

DR RICHARD DALY: For the induction agents?

DR SUDHIR KUSHWAHA: Yes.

DR RICHARD DALY: Yes. It's controversial, really, isn't it?

DR SUDHIR KUSHWAHA: Yes.

DR RICHARD DALY: We feel like we can rely on it and that it has the advantages of protecting the kidneys and being very reliable for eliminating cell-mediated rejection. But other programs prefer to go ahead with calcineurin inhibitors in the operating room, and their protocols have been very successful for them. I think that we learn our immunosuppression protocol at our [own] institution. We understand what the risks and limitations are, and then we are able to manage the patients with a good understanding of our protocol. Others would use different protocols but also understand limitations of their [own] protocol, and all have had very good outcomes.

DR SUDHIR KUSHWAHA: That's correct. And then longer term, all patients end up on what we would call "triple immunosuppression," and that typically includes a calcineurin inhibitor. It used to be cyclosporine mostly, but I think most centers now are using tacrolimus [Prograf, Astellas] and mycophenolate and steroids, and the steroids typically
start off at a fairly high dose, which is a weight-adjusted dose. Then we try to do a relatively rapid taper, a tapering program prior to the patient being discharged. And that immunosuppression usually maintains the organ and prevents the acute rejection from occurring, although we still do see acute rejection, particularly in the early posttransplant period; within the first three to six months it's quite common.

The surveillance for rejection is the next topic we're going to talk about. We (and most centers) have historically relied on the use of the endomyocardial biopsy. There are [now] newer techniques that are being developed and being looked at; there have been a number of studies done. But I would still say that the endomyocardial biopsy remains the gold standard in terms of looking for rejection. Do you think that we rely on this too much, or do you think it still has a role, Rocky, in the present posttransplant management strategies?

DR RICHARD DALY: I think it remains an essential part of the strategy. I think there are other options, but we have not gotten away from the need for the gold standard, for sure.

DR SUDHIR KUSHWAHA: We typically look for cell-mediated rejection using the biopsy, but there's also what we call antibody-mediated rejection. What role do you think biopsy has in trying to predict antibody-mediated rejection? And if we have a negative biopsy and a failing heart, how do we look at that patient?

DR RICHARD DALY: Of course, we try to avoid antibody-mediated rejection at the time of transplant because nowadays we know the [human leukocyte antigen] HLA type of our donor, and we know antibodies that the recipient has. We can virtually cross-match the donor and recipient prior to accepting a heart. But if we do encounter rejection that we can't explain on the basis of cellular infiltrates—that is, organ dysfunction after transplantation and biopsy not showing cellular infiltrates—then we've assumed that this was related to antibodies in the past.

We have staining techniques such as C4d stain to try to diagnose antibody-mediated rejection, but sometimes it's a clinical diagnosis where we don't have another explanation for a graft dysfunction late, isn't that right?

DR SUDHIR KUSHWAHA: No, I think that's the key point. I think if we see a patient whose cardiac function drops posttransplant and we don't see any evidence of cell-mediated rejection or any evidence under the microscope that there's a cellular infiltrate causing damage to the myocardium, then we suspect that it's probably antibody-mediated rejection and sometimes that's correlated with elevated circulating antibodies or donor-specific antibodies, which we refer to them as, which are elevated and can be measured in the bloodstream and that is sometimes supportive evidence.

In any case, we still cover the patient for both cell-mediated and antibody-mediated rejection, but the typical treatment for cell-mediated rejection is intravenous, high-dose steroids, typically methylprednisolone. But once that's been given, if we do have evidence that there might be circulating elevated antibody levels, there are other agents we can give as well as doing plasmapheresis—which is basically a way of removing those circulating antibodies from the circulation to try to decrease the immune assault from them, and then we would back that up with other agents.
Many of these therapies are experimental at this point but seem to have a role, including drugs that act against the B cells. I think the scope of this presentation doesn't allow too much of a detailed discussion about that, but I think that we're learning as we go along, wouldn't you say, Rocky?

DR RICHARD DALY: For sure, in this area. It's changing all the time. Let me ask you about the role of sirolimus because you've been a leader in using sirolimus and changing patients to this. We try to wean the steroids, but we pay a price with the calcineurin inhibitors over time. You've been a leader in the nation in changing patients over to sirolimus. Can you talk about that for a few minutes?

DR SUDHIR KUSHWAHA: Yes. The two main problems following transplantation, once they're over that acute first six months, I would say, is the long-term morbidity of renal dysfunction, which is a side effect of calcineurin-inhibitor therapy.

When I looked at our population several years ago, 11% of our heart-transplant population were either on the renal-transplant waiting list or undergoing dialysis. That's a significant number, and patients who weren't in that category had a significant degree of renal dysfunction. Sirolimus does not act through the same pathway. It's what's called an "mTOR inhibitor," a "mammalian target of rapamycin inhibitor." It suppresses T cells using a different mechanism and doesn't cause direct toxicity to the kidneys.

We initially adopted a strategy of trying to switch patients over, and we have shown through our studies that the degree of rejection didn't increase and their kidney function got better, and that was an immediate benefit of using that drug.

The long-term benefit we've also looked at and published in a couple of papers is the benefit on allograft vasculopathy. Allograft vasculopathy is a diffuse coronary disease that affects the transplanted heart and it's really the direct result of a chronic immune assault (low grade) that happens over time to the transplanted heart and results in endothelial dysfunction, intimal proliferation, and smooth-muscle hypotrophy, [which means] that the coronary arteries gradually become narrowed over time.

If we look at the coronary angiogram of a patient who's over five years out and compare it with their baseline study, we will see that the coronaries are significantly narrowed in terms of their diameter and often in terms of a decrease in their blood flow, as well.

Sirolimus is a powerful antiproliferative agent, and it seems to stop the proliferative process and attenuate allograft vasculopathy. In fact, our most recent study, which was published earlier this year, we demonstrated that over a four-year period there's really no significant change in intimal thickening compared with controls who have been maintained on calcineurin inhibitors.

We think is that this is going to have a role in prolonging overall survival because ultimately, the biggest cause of mortality after heart transplant is actually allograft vasculopathy. If we look at the historical survival figures from the [International Society for Heart & Lung Transplantation] ISHLT, we see that there's about a 50% 10- to 15-year survival rate. I say 10 to 15 because some of that data are historical and from the early days of transplant.
We really think it's an important part of the immunosuppressive strategy to the extent that in our population we've adopted a strategy of trying to convert most patients by six months. The reason we have picked six months is that this drug is a powerful antiproliferative—we want to make sure that all the wounds are appropriately healed and that there are no other issues going on and that the patient is at a stable point.

DR RICHARD DALY: Thanks, Sudhir. I think we're low on time now and we'll wrap this up for today. We certainly appreciate everybody's attention.

DR SUDHIR KUSHWAHA: Thank you, Rocky. I think it's been a great discussion. I hope we've covered all the major points related to heart transplantation. Thank you.

DR RICHARD DALY: Thank you.