Title

Intracoronary radiation to treat in-stent restenosis in six cardiac transplant patients

Journal

Catheterization and Cardiovascular Interventions, 60(1)

ISSN

1522-1946

Authors

Grise, Mark A
Reilly, John P
Tobis, Jonathan M
et al.

Publication Date

2003-09-01

DOI

10.1002/ccd.10607

Catheterization and Cardiovascular Interventions 60:41–44 (2003)

Intracoronary Radiation to Treat In-Stent Restenosis in Six Cardiac Transplant Patients

Mark A. Grise,[1] MD, John P. Reilly,[1] MD, Jonathan M. Tobis,[2] MD, Yuzuru Takano,[2] MD, Jesse W. Currier,[2] MD, Jon A. Kobashigawa,[2] MD, Giora Weisz,[3] MD, Jeffrey W. Moses,[3] MD, Martin B. Leon,[3]MD, Alan Yeung,[4] MD, and Paul S. Teirstein,[1*†] MD

Transplant vasculopathy significantly limits the survival of cardiac transplant patients and occurs in 50% of patients by 5 years posttransplant. We report our experience with six cardiac transplant patients who underwent intracoronary brachytherapy for in-stent restenosis. At four centers, six patients underwent intracoronary radiation for in-stent restenosis. All patients received extended antiplatelet therapy with clopidogrel and aspirin. Follow-up angiography was performed in all patients. Two of the six patients underwent subsequent target lesion revascularization. Patient 1 presented with total occlusion of her radiated lesion. She had a complex procedure requiring stenting for a dissection after the radiation dwell. Patient 2 had high-grade restenosis following brachytherapy. Patient 3 had a 50% restenotic lesion. Patients 4, 5, and 6 had follow-up angiography that showed no evidence of restenosis. There are few good options to treated accelerated transplant vasculopathy. Radiation therapy may be a viable option in this difficult patient population. ***Catheter Cardiovasc Interv 2003;60:41–44.***

Key words: radiation; restenosis; transplantation; angioplasty

INTRODUCTION

Cardiac allograft vasculopathy (CAV) is the leading cause of death in heart transplant recipients and a frequent cause of retransplantation. Its prevalence, as detected by angiography, is 40–50% by 5 years posttransplant, and in some autopsy studies 100% of patients show some evidence of transplant vasculopathy [1–3]. There is limited effective medical therapy for CAV; diltiazem, pravastatin, and simvastatin demonstrated only moderate efficacy [4–6]. Several small studies have evaluated the role of angioplasty and stenting for the treatment of CAV; however, this approach is limited by high rates of restenosis [7–10].

Intracoronary radiation is a well-established treatment of in-stent restenosis in nontransplanted patients [11–15]. The objective of this report is to describe the outcome following intracoronary radiation therapy for in-stent restenosis in heart transplant patients.

CASE REPORTS

A total of six patients were treated at four institutions (two each at Scripps Clinic and UCLA Center for Health Sciences, and one each at Lenox Hill and Stanford University). Prior to coronary radiation, five of the six patients were treated with the Cutting Balloon (Scimed, Maple Grove, MN) and one patient was treated with the FX Minirail (X-Technologies, Tustin, CA) to achieve an adequate lumen with a $\leq$ 10% residual stenosis. One patient received a new stent at the time of radiation for an edge dissection. Patients received either gamma radiation (Cordis, Miami, FL; three patients) or beta radiation (Novoste, Norcross, GA; three patients), depending on operator preference and institutional availability. All pa-

[1]Division of Cardiovascular Disease, Scripps Clinic, La Jolla, California
[2]Division of Cardiology, University of California, Los Angeles, California
[3]Cardiovascular Research Foundation, Interventional Cardiology at Lenox Hill Hospital, New York, New York
[4]Division of Cardiovascular Disease, Stanford University, Stanford, California

[†]In accordance with the policy of the Journal, the designated author discloses a financial or other interest in the subject discussed in this article.

Received 29 November 2002; Revision accepted 22 April 2003

*Correspondence to: Dr. Paul S. Teirstein, Division of Cardiovascular Diseases, Scripps Clinic, 10666 North Torrey Pines Road, La Jolla, CA 92037. E-mail: radman@scrippsclinic.com

DOI 10.1002/ccd.10607
Published online in Wiley InterScience (www.interscience.wiley.com).

TABLE I. Baseline Characteristics

Patient	Age	Sex	Years from transplantation to radiation	Reason for transplantation	Number of previous restenoses	Diabetes
1	55	F	9	Idiopathic dilated	2	No
2	58	M	7	Familial cardiomyopathy	3	No
3	27	M	5	Familial cardiomyopathy	1	No
4	74	M	8	Valvular cardiomyopathy	2	No
5	61	M	10	Ischemic cardiomyopathy	2	No
6	53	M	16	Idiopathic dilated	0	No

TABLE II. Outcomes and Treatment Characteristics

Patient	Vessel	Days from radiation to follow-up angiogram	Target lesion revascularization	Vessel diameter (mm)	Radiation source	Length of radiation source (mm)
1	RCA	119	Yes	3.75	Sr^{80}/Y^{90}	40
2	LAD	251	Yes	3	Ir^{192}	71
3	PDA	204	No	3	Sr^{80}/Y^{90}	40
4	LAD	263	No	2.75	Ir^{192}	39
5	LCx	154	No	3.5	Ir^{192}	55
6	LAD	231	No	3.5	Sr^{80}/Y^{90}	30

tients were prescribed extended antiplatelet therapy ($\geq$ 6 months) with clopidogrel and aspirin. Follow-up was obtained by reviewing all medical records, subsequent angiograms, procedures, and patient phone contact.

RESULTS

Between December 2000 and October 2001, six cardiac transplant recipients at four institutions were treated with intracoronary radiation to treat in-stent restenosis. Baseline clinical characteristics of the six patients are displayed in Table I. All six patients had follow-up angiography.

Of the six patients, two (33.3%) underwent subsequent target lesion revascularization (Table II). Patient 1 underwent intracoronary radiation to the right coronary artery. At the time of her radiation therapy, a new stent was placed at the radiation site to treat an edge dissection that was discovered following the radiation dwell. She received aspirin and clopidogrel as prescribed. She presented 119 days following radiation with increasing dyspnea. Angiography revealed a complete occlusion of the right coronary artery at the previously irradiated site. There was no myocardial infarction. She was treated with intravenous abciximab and balloon dilatation. Patient 2 underwent intracoronary radiation of his left anterior descending artery. At 251 days posttreatment, angiography performed for increasing dyspnea revealed that the LAD was subtotally occluded at the irradiated area. Two months later, he received rapamycin-eluting stents as part of a compassionate use protocol. Patient 3 underwent follow-up angiography at 204 days, which revealed a 50% diameter stenosis within the radiation segment that was not intervened on. The patient was asymptomatic and doing well. Patient 4 underwent radiation to his LAD. He returned for follow-up angiography at 263 days and no renarrowing was observed. Patient 5 underwent radiation to the left circumflex. He had angiography at 154 days, which revealed no evidence of restenosis in the target vessel. Patient 6 underwent radiation to the proximal LAD. His follow-up angiogram at 231 days showed no evidence of restenosis, and clinically he was asymptomatic.

DISCUSSION

CAV is the leading cause of morbidity in transplant recipients and there are currently no satisfactory therapeutic options to treat this entity [1–3]. CAV manifests as an accelerated form of coronary disease affecting both intramyocardial and epicardial arteries. Rapid development of CAV within 1 year of transplantation portends a poor prognosis and is associated with a high rate of major clinical events [16]. Most transplanted patients do not experience anginal pain; thus, the first clinical manifestations of CAV are often congestive heart failure, ventricular arrhythmias, or sudden death [17]. At 1, 2, and 4 years posttransplantation, the incidence of angiographically visible CAV is 11%, 22%, and 45%, respectively. Intimal thickening can be detected with the use of intravascular ultrasound in up to 75% of transplanted patients by 1 year [16,18].

Several groups have reported success using percutaneous therapies, including stenting, to treat obstructive

allograft vasculopathy. Sandhu et al. [9] reported the outcomes of eight transplanted hearts undergoing 10 successful PTCA procedures. Six of these 10 lesions were studied angiographically 4 or more months after PTCA. One was restenosed, and one could not be evaluated due to complete occlusion of the proximal vessel. The other four PTCA sites were patent, without significant restenosis. Four of the eight patients died between 3 and 36 months postprocedure (three sudden deaths and one due to progressive heart failure), underscoring the high mortality in patients with CAV.

Thirteen medical centers retrospectively analyzed their experience with percutaneous coronary angioplasty, directional coronary atherectomy, and coronary artery bypass surgery in transplant patients [10]. Coronary angiography was undertaken in 66 patients. Angiographic success ($<$ 50% residual stenosis) was achieved in 153 (94%) of 162 lesions; however, there were two periprocedural deaths due to myocardial infarction. Atherectomy was successfully performed in 9 (82%) of 11 lesions, but there were two periprocedural deaths. Bypass surgery was undertaken in 12 patients. Four patients died perioperatively and seven patients were alive at 9 ± 7 months after the operation. Forty (61%) of the 66 patients were alive without retransplantation at 19 ± 14 months after percutaneous interventions. Angiographic restenosis occurred in 42 (55%) of 76 lesions at follow-up of 8 ± 5 months. Angiographic evidence of distal arteriopathy was found to affect allograft survival adversely.

Redonnet et al. [7] reported their experience in nine patients who had 37 lesions treated percutaneously: 22 treated with balloon angioplasty and 15 treated with stent implantation. Six-month angiographic follow-up was obtained in eight of the nine patients. Restenosis rates were 67% with balloon angioplasty and 64% with stenting.

Intracoronary radiation is now a widely used modality to treat in-stent restenosis [11–15]. There has been one previous report of successful treatment of in-stent restenosis with brachytherapy in a cardiac transplant patient but no follow-up was reported [19]. Neointimal hyperplasia results mainly from proliferation of smooth muscle cells and extracellular matrix secretion. CAV appears to be a chronic inflammatory response to immune-mediated injury. Smooth muscle cell proliferation and subcellular matrix deposition occurs in a manner similar to the mechanism of in-stent restenosis. Thus, intracoronary brachytherapy may be uniquely suited to treat not only in-stent restenosis, but also CAV itself in transplant recipients.

The present report documents the largest cohort to date of transplant patients treated with intracoronary radiation. All patients had follow-up angiography. Two of the six (33.3%) patients failed radiation therapy and underwent subsequent target lesion revascularization. One of these patients underwent a complex procedure including placement of a new stent for a dissection at the time of radiation treatment. This patient presented with total occlusion at follow-up. While cardiac enzymes did not reveal evidence of myocardial infarction, thrombosis may have been the cause of late failure in this patient despite aspirin and clopidogrel. The other patient presented with a subtotal occlusion of his radiated segment and ultimately received rapamycin-eluting stents.

Intracoronary brachytherapy appears feasible and safe in this small cohort of transplanted patients with in-stent restenosis. However, failure in two (33.3%) patients highlights the need for further study and a search for even more effective therapies for this challenging group of patients.

REFERENCES

1. Barnhart GR, Pascoe EA, Mills AS, et al. Accelerated coronary atherosclerosis in cardiac transplant patients. Transplant Rev 1998;1:31–46.
2. Gao SZ, Alderman EL, Schroeder JS, et al. Accelerated coronary vascular disease in the heart transplant patient: coronary arteriographic findings. J Am Coll Cardiol 1988;12:334–340.
3. Weis M, von Scheidt W. Cardiac allograft vasculopathy: a review. Circulation 1997;96:2069–2077.
4. Kobashigawa JA, Katznelson S, Laks H, et al. Effects of pravastatin on outcomes after cardiac transplantation. N Engl J Med 1995;333:621–627.
5. Wenke K, Meiser B, Thiery J. Simvastatin reduces graft vessel disease and mortality after heart transplantation: a four year randomized trial. Circulation 1997;96:1398–1402.
6. Schroeder JS, Gao SZ, Alderman EL. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. N Engl J Med 1993;328:164–170.
7. Redonnet M, Tron C, Koning F, et al. Coronary angioplasty and stenting in cardiac allograft vasculopathy following heart transplantation. Transplant Proc 2000;32:463–465.
8. Heublein B, Pethig K, Maab C, et al. Coronary artery stenting in cardiac allograft vascular disease. Am Heart J 1997;134: 930–938.
9. Sandhu JS, Uretsky BF, Reddy PS, et al. Potential limitations of percutaneous transluminal coronary angioplasty in heart transplant recipients. Am J Cardiol 1992;69:1234–1237.
10. Halle AA, DiSciascio G, Massin EK, et al. Coronary angioplasty, atherectomy and bypass surgery in cardiac tranplant recipients. J Am Coll Cardiol 1995;26:120–128.
11. Teirstein PS, Massullo V, Jani S, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med 1997;336:1697–1703.
12. Waksman R, White LR, Chan RC, et al. Intracoronary γ-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000;101:2165–2171.
13. Al-Bassam M, Robertson LM, Passamani E. Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981: the National Heart, Lung, and Blood Registry. N Engl J Med 1988; 318:265–270.

14. Leon MB, Teirstein PS, Moses JW, et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. N Engl J Med 2001;334:250–256.
15. Waksman R, Raizner AE, Yeung AC, et al. Use of localized intracoronary beta radiation in treatment of in-stent restenosis: the inhibit randomized controlled trial. Lancet 2002;359:543–544.
16. Yeung AC, Davis SF, Hauptmann PJ, et al. Incidence and progression of transplant coronary artery disease over 1 year: results of a multicenter trial with use of intravascular ultrasound. J Heart Transplant 1995;14:S215–S220.
17. Gao SZ, Schroeder JS, Hunt SA, et al. Acute myocardial infarction in cardiac transplant recipients. Am J Cardiol 1989;64:1093–1097.
18. Costanzo MR, Naftel DC, Pritzker MR, et al. Heart transplant coronary disease detected by angiography: a multi-institutional study. J Heart Lung Transplant 1996;15:S39.
19. Thew ST, Snell RJ, Klein LW. First use of intracoronary beta-radiation to prevent recurrent in-stent restenosis in a transplanted heart. Catheter Cardiovasc Interv 2002;55:373–375.