Durable Clinical Benefit Following Sr^{90} Beta Irradiation Therapy for In-Stent Restenosis in High-Volume Community Practice

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Post angioplasty restenosis is a major limitation of percutaneous coronary intervention that has been significantly reduced with the widespread application of stents.[1,2] Coronary stents are now used in approximately 80-90% of all interventional cardiology procedures.[3] The proliferation of stent use has been the result of several factors including a documented decrease in restenosis rates compared to conventional angioplasty; the achievement of a stable, predictable, angiographic result even in complex lesions; a decreased need for urgent or emergency coronary bypass graft surgery; and the reliable treatment of acute or threatened abrupt vessel closure resulting from conventional angioplasty. Despite these major mechanical advantages, stents have some disadvantages the most significant of which is late in-stent restenosis (ISR).

While coronary stenting has progressively evolved with improvement in stent design and deployment strategies, the treatment of ISR remains a clinical challenge. Lesion length and vessel size are recognized predictors of recurrent restenosis with the highest rates found in diffuse lesions (> 10 mm) and in smaller compared to larger vessels.[4-8] Elastic recoil of the vessel and negative remodeling have been effectively treated with coronary stents, but the neointimal hyperplasia and matrix deposition that follows deep arterial wall injury is exaggerated compared to balloon angioplasty alone. Intracoronary radiation therapy (ICRT) reduces angiographic and clinical restenosis in patients with ISR by approximately 50% compared to balloon angioplasty alone and is currently the most widely used modality for treatment of this novel pathobiological problem.[9-14]

METHODS

Consecutive percutaneous coronary interventions performed at The Christ Hospital in Cincinnati, Ohio from January 1, 2001 through June 30, 2002 were analyzed (n = 3,869) for the use of ICRT for treatment of ISR. A total of 330 patients during this time underwent coronary irradiation for ISR performed by 10 different operators. All intracoronary radiation cases were included irrespective of target site or radiation source. Fifty-three patients were treated with Ir^{192}; 12 patients with P^{32}, and 265 with the Novoste Sr^{90} Beta-Cath System. Baseline demographics of the 265 patients treated with the Novoste System are shown in Table 1. There was nearly an equal number of males and females (male 55%, female 45%) and diabetes was present in 40% of patients.

Device and procedure description. The Novoste Sr^{90} Beta-Cath System has 2 principal components: the delivery catheter for the jacketed radiation source train and the hand-held, hydraulic, radiation transfer device delivery system (Figure 1). Strontium (Sr^{90}) in both the 30 mm and 40 mm source trains was used with both the 5 French (Fr) over-the-wire and 3.5 Fr monorail delivery catheters. After baseline coronary

angiography, percutaneous transluminal coronary revascularization was performed according to standard clinical practice. Successful PCI was defined as a residual stenosis of <50% and an increase in lumen diameter of >25%. Restenting of the target site was discouraged and 10% (27/265) received additional stents immediately prior to ICRT. The delivery catheter for the Novoste system was then positioned at the angioplasty site and the appropriate radiation source train was deployed for the period of time determined to deliver the prescribed dose at 2 mm. Following treatment, the radiation source train was removed by manual hydraulic pressure from the transfer device and the catheter delivery system was removed. Follow-up angiography was performed to demonstrate an adequate result prior to procedure termination.

Table 1. Baseline demographic and clinical characteristics of Novoste-treated patients (n = 265)

Age — mean (range)	63 years (35–90)
Male	55% (145/265)
Female	45% (120/265)
Diabetes mellitus	40% (107/265)
Hypertension (on medication)	60% (160/265)
Hyperlipidemia	53% (140/265)
Cigarette smoking	45% (119/265)

Figure 1. *Picture of the Novoste Sr90 transport device and catheter.*

Table 2. ISR lesion type and original stent diameter and length of the 265 patients treated with ICRT

Lesion Type	
Single lesion	67% (177/265)
Multi-lesion	17% (45/265)
Multi-vessel	10% (27/265)
SVGs	6% (16/265)
Stent size	
Diameter:	
2.5mm	15% (40/265)
3.0mm	45% (118/265)
3.5mm	26% (70/265)
4.0mm	14% (37/265)
Length:	
≤ 12mm	11% (30/265)
12–15mm	18% (47/265)
15–18mm	23% (60/265)
18–24mm	28% (73/265)
≥ 24mm	21% (55/265)

SVG = saphenous vein graft

All patients were pretreated with aspirin (325 mg) prior to the procedure and received clopidogrel immediately following the procedure (300 mg oral load, if not already on clopidogrel, then 75 mg daily). An activated clotting time was maintained at 200-250 seconds during the intervention if adjunctive platelet glycoprotein (GP) IIb/IIIa inhibition was used, or 250-300 seconds without additional GP IIb/IIIa anti-platelet therapy by the use of unfractionated heparin. Clopidogrel therapy was maintained for at least 1 year following radiation therapy. Clinical follow-up was at the discretion of the primary cardiologist according to standard clinical guidelines.

RESULTS

The Novoste Sr^{90} Beta-Cath System was successfully deployed to the target site in 265 of 270 (98%) of patients with ISR. The 5 failures were due to an inability to pass the 5 Fr radiation delivery catheter to the site of intervention primarily due to the profile of the system not allowing the device to track to the site of ISR. All 270 were successfully treated with conventional angioplasty. Forty-five of the 265 successfully treated patients (17%) were multilesion interventions for ISR that included radiation treatment ≥ 2 sites within the target vessel. Twenty-seven of the 265 patients (10.0%) were multivessel interventions for ISR that included more than 1 target vessel, and 16 of the 265 patients (6.0%) included saphenous vein graft interventions for ISR (Table 2). Data on the original stent deployed (diameter and length) in these 265 patients undergoing subsequent therapy for ISR is shown in Table 2. Consistent with findings from previous studies, smaller diameter stents with longer length made up the larger proportion of ISR lesions in this patient population.

At a mean follow-up of 10.5 ± 2.8 (SD) months, 53 patients (20%) had returned for evaluation secondary to symptoms of unstable angina. Follow-up angiography was performed in all 53 of these patients and compared to the immediate post-radiation angiogram following Novoste Sr90 therapy for ISR. Of these 53 patients, twenty-three had repeat PCI procedures for symptoms of unstable angina. These included: two target site revascularizations (TSR) performed for apparent radiation treatment failure; twelve non-TSR performed for new obstructive disease outside the initial radiated segment within the same target vessel; and 9 non-target vessel revascularizations (TVR) representing new obstructive disease within a different vessel other than the initial radiated artery. In addition, out of the 53 patients who returned for symptoms, coronary artery bypass surgery was performed in 11 total patients. Four patients had progressive disease within the target site (TSR) and 7 patients had progressive disease outside the target vessel (non-TVR) requiring surgical revascularization. Overall, analyzing the 53 patients that returned for clinical symptoms out of the original 265 patients treated for ISR, the clinical TSR rate was 2.3% with a TVR rate of 6.8% (Table 3).

DISCUSSION

Restenosis is a problem of exaggerated healing in the coronary artery after mechanical injury, with smooth muscle cell migration and proliferation causing luminal compromise in association with a lack of compensatory vessel wall dilation.[15] Following balloon angioplasty, geometric remodeling is a critical response with up to 70% of late loss due to chronic vessel constriction.[16] Stents provide a scaffold for the vessel wall, and largely eliminate this pathologic remodeling. Serial Intravascular ultrasound (IVUS) studies in stented lesions show that most late loss is due to neointimal proliferation distributed over the length of the stent.[17] Longer lesions with greater plaque burden provide an increased source of smooth muscle cells that proliferate to form neointimal.[18] Stenting elicits a relatively higher proliferative response in small vessels perhaps secondary to a relatively higher degree of vessel wall stretch thus creating more injury.

Use of ICRT has been shown to reduce neointimal lesion formation following arterial injury in a variety of animal models.[19] Targeting the adventia with an effective dose of radiation to inhibit the proliferation of adventitial myofibroblasts is one proposed mechanism of restenosis. Adjunctive ICRT after angioplasty has been shown to be efficacious with an approximate 50% reduction in angiographic restenosis and a 60% reduction in major adverse cardiac events (MACE) at 3-year-follow-up.[20] IVUS analysis has shown that intimal hyperplasia is reduced with ICRT compared to placebo treated controls and that lesion length and vessel diameter are important predictors in assessing risk of recurrent ISR.[21,22]

Our results from this cohort of patients are consistent with randomized clinical trials demonstrating the efficacy of ICRT for the treatment of ISR. The patient demographics reflect the typical profile seen in a large volume clinical practice. Of note, the percentages of female patients and those with diabetes mellitus appear higher than those included in randomized clinical trials and may represent a higher risk sub-group for the development of recurrent ISR. In addition to the demographic and clinical characteristics of this patient population, the lesion type treated with ICRT reflects the broad spectrum of "real world" interventional cardiology practice. Single lesion ICRT accounted for 67% of the patients treated while a significant portion had multilesion (17%), multivessel (10%) or saphenous vein graft (6%) interventions for ISR. Consistent with prior observations, smaller diameter stents and longer stent length comprised a larger proportion of the patients treated with ICRT for ISR.

Over a follow-up period of nearly 1 year, 20% of the 265 patients treated for ISR with ICRT returned for symptoms that required repeat angiography; 8.7% had repeat PCI and 4.2% underwent coronary artery bypass surgery (CABG). Of the patients undergoing revascularization procedures (n = 34), 6 (17.6%) were TSR and 28 (82.4%) were non-TSR. Overall analysis of the 265 ICRT patients demonstrated a TSR rate of 2.3% and a TVR rate of 6.8%. Thus, the development of coronary obstruction at sites distinct from the original ICRT target prompted angiography and revascularization in the majority of cases.

Secondary preventative strategies with anti-platelet agents have been shown to reduce the incidence of subacute stent thrombosis in patients with ISR treated with ICRT. Current recommendations for anti-platelet therapy call for 6 months of clopidogrel therapy following ICRT for ISR.[23] Importantly, three of the patients who required repeat PCI in this patient cohort had discontinued their clopidogrel therapy between 6 months and 1 year after ICRT. These were either protocol driven discontinuations (after 6 months of therapy) or secondary to planned surgical procedures. Shortly after discontinuation of anti-platelet therapy, these patients presented with symptoms of an acute coronary syndrome requiring repeat angiography. All 3 of these patients had recurrent disease at the site of ICRT with angiographic evidence of thrombus and were successfully treated with repeat PCI and adjunctive platelet GP IIb/IIIa anti-platelet therapy.

Vascular brachytherapy (VBT) is associated with a dose-dependent increase in luminal thrombus that may persist for months following treatment.[24] Re-endothelialization is delayed by VBT and vascular healing may take several months following ICRT for ISR.[25] Clinical factors that contribute to late stent thrombosis following VBT include re-stenting at the time of the radiation procedure and

discontinuation of thienopyridine therapy. Although evidence based support for sound recommendations regarding the duration of clopidogrel therapy are lacking, anecdotal case-based reports, as well as the current experience, have helped define our current long-term approach.[26] In uncomplicated VBT procedures without resenting, combined aspirin and clopidogrel therapy is continued for a minimum of 6 months and probably indefinitely in patients who are tolerant of this therapy.[27] In patients requiring complex or re-stenting procedures, combination anti-platelet therapy is continued indefinitely with only brief (4-5 days) interruptions in therapy for surgical procedures. Heightened vigilance should accompany any discontinuation of anti-platelet therapy in high risk patient populations. Based on current secondary preventative data with clopidogrel, a "life-long" treatment approach may be warranted in this patient population.[28,29]

CONCLUSION

Instent restenosis remains a significant problem that can result in the need for repeat PCI procedures and even coronary bypass surgery. ICRT remains the only proven therapeutic strategy for treating patients with ISR. Evolving technology with thin-strut cobalt-chromium stents and drug-eluting stents which provide lower rates of ISR, may ultimately reduce the need for ICRT. However, many "unknowns" remain for these evolving technologies and ICRT represents an FDA approved treatment modality for ISR with established clinical and economic benefit that should not be discarded prematurely. Our results demonstrate a durable clinical benefit with ICRT for ISR across the wide spectrum of "real world" interventional cardiology patients. Procedural success rates are high and TSR/TVR are low following Novoste Sr^{90} therapy. Prolonged anti-platelet therapy ($\geq$ 1 year) seems prudent and other aggressive secondary preventative measures are important to maintain long-term procedural success.

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