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International Journal of Cardiology 99 (2005) 201–205

International Journal of Cardiology

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Long-term outcomes after treatment of diffuse in-stent restenosis with rotational atherectomy followed by beta-radiation therapy with a ^{188}Re-MAG$_3$-filled balloon

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Received 22 August 2003; received in revised form 27 December 2003; accepted 28 December 2003
Available online 15 April 2004

Abstract

Background: Intracoronary radiation therapy for in-stent restenosis has been demonstrated to reduce restenosis and major adverse cardiac events. However, long-term angiographic and clinical outcomes after beta radiation therapy have not been sufficiently evaluated. *Methods:* We evaluated the long-term angiographic and clinical outcomes of 50 consecutive patients who had received beta-radiation therapy with a ^{188}Re-MAG$_3$-filled balloon after rotational atherectomy for diffuse in-stent restenosis (lesion length>10 mm) in native coronary arteries. The radiation dose was 15 Gy at a depth of 1.0 mm into the vessel wall. *Results:* The mean lesion length was 25.6 ± 12.7 mm. Radiation was delivered successfully to all patients without any procedural or in-hospital complications. At the 6-month angiogram, the restenosis rates was 10% (5/50). There were no major adverse cardiac events (MACE), such as death, myocardial infarction, and target lesion revascularization (TLR) by 6-month follow-up. Long-term clinical follow-up data were obtained in all patients during 30.1 ± 4.5 months. No myocardial infarction and one noncardiac death occurred during follow-up. Two-year follow-up angiogram was performed in 26 (58%) of 45 patients who showed a patent radiation segment at the 6-month angiogram. Significant narrowing of diameter stenosis of more than 50% occurred in 6 (23%) of 26 patients between 6 and 24 months after beta-radiation. Late TLR was performed in 6 patients. The rate of 30-month death-free survival and MACE-free survival were 98.0 ± 2.0% and 86.9 ± 5.0%. *Conclusion:* Beta-radiation using a ^{188}Re-MAG$_3$-filled balloon after rotational atherectomy is associated with favorable long-term angiographic and clinical outcomes.

Keywords: In-stent restenosis; Radiation therapy; Rotational atherectomy

1. Introduction

Previous studies have demonstrated that stenting for a de novo lesion provides improved short-and long-term clinical outcomes compared to balloon angioplasty [1,2]. However, in-stent restenosis (ISR) remains a major limitation of stent technology and represents a technical challenge to the interventional cardiologist [1–4]. Previous studies have reported a high incidence of recurrent restenosis after conventional treatment such as repeat balloon angioplasty, repeat stenting, and rotational atherectomy for ISR, and especially for diffuse ISR [5–9]. Several clinical studies have evaluated the efficacy of intracoronary radiation for ISR using gamma and beta emitters, and demonstrated favorable outcomes in terms of recurrent restenosis and major adverse cardiac events [10–12]. Previously, we also have reported that beta-radiation using a ^{188}Re-mercaptoacetyltriglycine (MAG$_3$)-filled balloon after rotational atherectomy improved clinical and angiographic outcomes in the R^4 registry [13]. However, the long-term efficacy and safety of this treatment modality are unknown, and there are concerns of late thrombosis, so called late catch-up, and aneurysm formation. In this present study we prospectively evaluated the long-term clinical and angiographic outcomes (2 years) of intracoronary beta-radiation therapy with a ^{188}Re-MAG$_3$-filled balloon after rotational atherectomy in patients with diffuse ISR (R^4 registry).

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doi:10.1016/j.ijcard.2003.12.035

2. Methods

Fifty consecutive patients (42 men, age 56 ± 9 years) were enrolled in this study. The baseline clinical and angiographic characteristics are listed in Table 1.

2.1. Study group and procedure

The methods uesd have been described previously [13]. This study was approved by our Institutional Review Board. Fifty consecutive patients with diffuse ISR were prospectively enrolled at Asan Medical Center between March 1999 and February 2000. Patient inclusion criteria were diffuse ISR (lesion length>10 mm, diameter stenosis>50%) in a native coronary artery with angina, demonstrable myocardial ischemia and written, informed consent. Exclusion criteria were acute myocardial infarction within 72 h, poor renal function (serum creatinine ≥ 3.0 mg/dl), pregnancy, contraindication to antiplatelet therapy and concomitant serious disease with an expected survival of less than 2 years. Additional new stent implantation was strongly discouraged, although not contraindicated. Before radiation therapy, rotational atherectomy and adjunctive percutaneous coronary angioplasty were performed to obtain an optimal angiographic result (diameter stenosis < 20%). The radiation time was calculated for the delivery of 15 Gy at a depth of 1.0 mm into the vessel wall from the balloon-artery interface. All patients were pretreated with aspirin (200 mg/day), ticlopidine (500 mg/day) and cilostazol (200 mg/day) for 2 days. Ticlopidine was given for 1 month, but aspirin and cilostazol were administrated indefinitely after irradiation [13].

Table 1
Baseline clinical and angiographic characteristics

Characteristics	$n = 50$
Age, years	56 ± 9
Male, %	42 (84)
Risk factors, %	
Hypertension	19 (38)
Diabetes mellitus	13 (26)
Total cholesterol ≥ 240 mg/dl	12 (24)
Current smoker	31 (62)
Prior myocardial infarction	8 (16)
Unstable angina	33 (66)
Left ventricular ejection fraction, %	60 ± 7
Rotablation procedure	
Mean burr size, mm	2.1 ± 0.2
Burr/artery ratio	0.7 ± 0.1
Artery treated, %	
Left main coronary artery	1 (2%)
Left anterior descending artery	34 (68%)
Left circumflex artery	5 (10%)
Right coronary artery	10 (20%)
Balloon/artery ratio	1.18 ± 0.14
Lesion length, mm	25.6 ± 12.7
Reference vessel diameter, mm	2.89 ± 0.40
Radiation therapy	
Length of irradiated segment, mm	37.6 ± 11.2
Overlap of two balloons	7 (14%)
Fractionation	6 (12%)
Exposure time, sec	202 ± 62

2.2. Quantitative coronary angiography (QCA) analysis

Coronary angiograms were analyzed by two experienced angiographers using an on-line QCA system (ANCOR version 2.0, Siemens, Germany). Angiographic measurements were made during diastole after intracoronary nitroglycerin administration, using the guiding catheter for magnification calibration. Single matched views with the worst minimal lumen diameter and reference vessel diameter were compared. The reference vessel defined as the vessel segment 5 mm proximal and distal to the radiation sources was also compared.

2.3. Clinical and agiographic follow-up

All patients were evaluated clinically during an outpatient visit at 1, 3 and 6 months, and then every 4 months after radiation therapy. Repeat coronary angiography was requested at 6 months and 2 years after radiation, or earlier if clinically indicated. Major adverse cardiac events, including death, nonfatal myocardial infarction and repeat revascularization, were evaluated. Myocardial infarction was diagnosed when cardiac enzymes were elevated threefold or greater, with chest pain lasting at least 30 min, or with the appearance of new electrocardiographic changes. The angiographic incidence of late restenosis at 2 years (diameter stenosis ≥ 50%) was evaluated by QCA. Assessment of binary restenosis at 2 years included only those patients who showed a patent radiation segment at 6-month follow-up angiogram. Irrespective of target lesion revascularization, five patients with restenosis at 6-month follow-up angiogram were excluded from the late restenosis analysis.

2.4. Statistical analysis

Categorical data are presented as frequencies. Continuous data are presented as mean ± SD. Comparison was performed with paired Student's *t*-test, and ANOVA with repeated measures using the Bonferroni correction for post-hoc analyses. *P*-value < 0.05 was considered statistically significant. Rates of event-free survival were studied with Kaplan–Meier analysis and are displayed as survival curves.

3. Results

3.1. Clinical follow-up

Clinical follow-up was obtained in all living patients during mean follow-up of 30.1 ± 4.5 months. Clinical outcomes of study patients are shown in Table 2. We previously

Table 2
Clinical outcomes of study patients

	At 6 months	At 6–30 months
Death	0	1 (2%)
Noncardiac	0	1 (2%)
Cardiac	0	0
Nonfatal myocardial infarction	0	0
Target lesion revascularization	0	6 (12%)
Repeat intervention	0	5 (10%)
Cardiac bypass surgery	0	1 (2%)
Late thrombosis	0	0
Combined events	0	7 (14%)

reported that all patients ($n=5$) with restenosis at 6-month angiogram did not receive repeat intervention because they had either mild angina ($n=3$) or absence of a perfusion abnormality on the thallium perfusion single-photon emission computed tomographic image (SPECT) ($n=2$) [13]. Of these, two patients who presented with progressive angina at 10 and 12 months after radiation had a more decreased minimal lumen diameter at repeat angiographic examination, which required target lesion revascularization, and another patient with a decrease of miminal lumen diameter at the 2-year angiogram underwent bypass surgery. The remaining two patients continued receiving on medical treatment.

Three of six patients with restenosis at the 2-year angiogram also received repeat intervention. Therefore, late target lesion revascularization was performed in a total of six patients (12%) between 6 months and at the end of follow-up. Among them, five patients who required repeat interventions during follow-up period were managed with cutting balloon angioplasty. A single late noncardiac death due to cancer occurred at 20 months after radiation. However, no patient suffered from myocardial infarction or late thrombosis during the follow-up period. The rate of 30-month death-free survival and major adverse cardiac events (death, nonfatal myocardial infarction and target lesion revascularization)-free survival were $98.0 \pm 2.0\%$ and $86.9 \pm 5.0\%$ (Fig. 1).

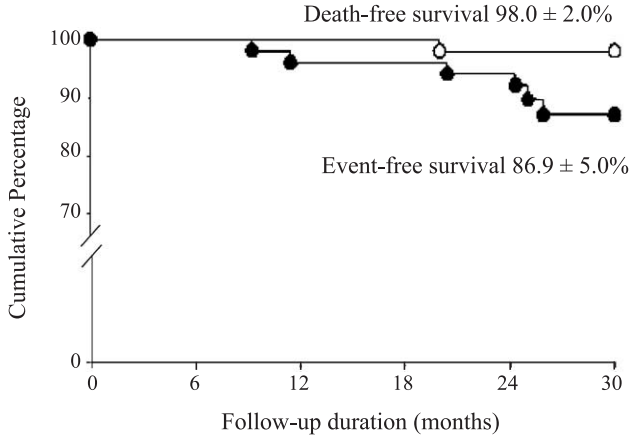

Fig. 1. Cumulative probability of survival free from any cause of death and target lesion revascularization.

3.2. Angiographic analysis

An initial follow-up angiogram after radiation therapy was obtained at a mean of 6.0 ± 2.0 months in all patients. At the 6-month angiogram, the restenosis rates was 10% (5/50). For this study, a late angiographic follow-up (2-year angiogram) was performed in 26 (58%) of 45 patients who showed a patent radiation segment at the 6-month follow-up angiogram. The remaining 19 patients who refused 2-year follow-up angiogram were free of angina. Among them, 16 patients underwent either thallium SPECT ($n=12$) or treadmill exercise test ($n=4$) at 2 years, the results of which were absences of abnormal perfusion or ST segment change. At the 2-year follow-up angiogram, restenosis, "late catch-up" occurred in six patients (23%, 6/26). The angiographic pattern of restenosis included one edge restenosis, one focal ISR, two diffuse ISRs, and two total occlusions. The patients who had total occlusion did not have any clinical symptoms of acute coronary syndrome. All of 6 patients with late restenosis at 2-year follow-up angiogram had geographic miss at the time of index procedure (two in the proximal, two in the distal and two in the both edges). However, the location of late restenosis at 2-year follow-up was the edge of irradiation in one patient and within the irradiated segment in five patients. Edge restenosis at 2-year follow-up in one patient occurred in the irradiated edge which was not associated with geographic miss.

QCA data were analyzed in 26 patients who underwent 6-month and 2-year follow-up angiogram. The minimal lumen diameter progressively decreased (2.68 ± 0.46 mm at postprocedure, vs. 2.31 ± 0.56 mm at 6 months, vs. 1.81 ± 0.43 mm at 2 years, respectively, $p<0.05$) (Fig. 2). A decrease in minimal lumen diameter was observed in 16 (61.5%) patients who underwent 2-year follow-up angiogram. When angiographic analysis was performed in 20 patients with a patent radiation segemnt at 2-year follow-up angiogram, there was a significant decrease in minimal

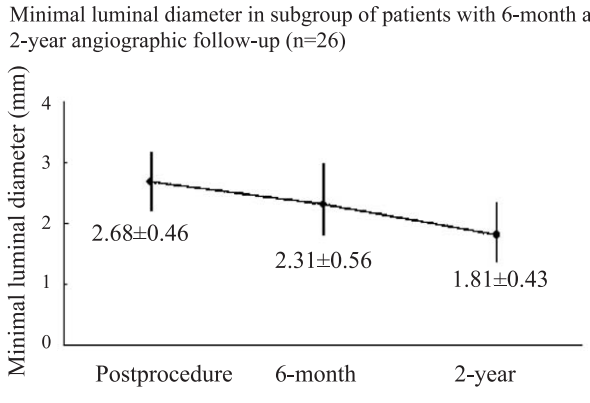

Fig. 2. Serial changes of minimal luminal diameter in selected patients with 6-month and 2-year angiographic follow-up who showed a patent radiation segment at 6-month follow-up angiogram. Postprocedure vs. 6 months, $p=0.018$; postprocedure vs. 2-year, $p=0.011$; 6-month vs. 2-year, $p<0.001$.

lumen diameter between postprocedure and 6-month follow-up (2.84 ± 0.41mm at postprocedure, vs. 2.38 ± 0.69 mm at 6 months, $p = 0.01$), but no significant decrease in minimal lumen diameter between 6-month and 2-year follow-up (2.26 ± 0.61 mm vs. 6-month follow-up, $p = 0.57$). Although the minimal lumen diameter progressively decreased in 26 patients who underwent 2-year follow-up angiogram, there was no significant change of reference vessel diameter between 6-month and 2-year (2.88 ± 0.40 mm at 6 months vs. 2.80 ± 0.43 mm at 2 years, $p = 0.56$). No aneurysm formation was observed between 6 months and 2 years.

4. Discussion

The major findings of this study are that (1) rotational atherectomy followed by beta-radiation using a ^{188}Re-MAG$_3$-filled balloon for diffuse ISR has favorable clinical and angiographic outcomes in terms of 6 months and 2 years angiographic restenosis and long term event-free survival and (2) the ''late catch-up'' phenomenon is present in some patients, which suggests that radiation delays the restenotic process.

Despite application of several percutaneous treatment modalities, the diffuse pattern of ISR has been reported to be associated with a high recurrence rate of restenosis [14–16]. Several recently published studies of intracoronary radiation therapy for ISR showed reductions in 6 months angiographic restenosis and target lesion revascularization compared with control group [11,12], and persistent long-term benefit of radiation therapy has been observed in other trials [17,18]. The Washington Radiation for In-Stent Restenosis Trial (WRIST) reported that gamma-radiation therapy with ^{192}Ir (15 Gy at 2 mm from the source) and beta-radiation therapy with ^{90}Y (20.6 Gy at 1 mm from the balloon surface) for diffuse ISR showed favorable outcomes in terms of target lesion revacularization and major adverse cardiac event at 2 years compared with control group [19]. The Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) trial also reported that target lesion revascularization at 3 years was significantly lower in ^{192}Ir patients than in placebo (15.4% vs. 44.8%, $p < 0.01$) [17]. In the current study, the rate of target lesion revacularization was 12% during mean follow-up duration of 30.1 ± 4.5 months. These results are consistent with the SCRIPPS trial. Our study included the uniform lesion subset of diffuse ISR, whereas the SCRIPPS trial had heterogenic lesion subsets including ISR, lesion not stented, and saphenous vein graft. Therefore, direct comparison between this study and the SCRIPPS trial would be difficult.

Three-year angiographic follow-up after intracoronary gamma-radiation was reported from the SCRIPPS trial. The restenosis rate was lower in the treated group than in the control group (33% vs. 64%, $p < 0.05$). A reduction in minimal lumen diameter by QCA analysis was observed at 3 years, which suggests that irradiation delays the restenosis process. These findings are similar to our results. In the present study, 2-year angiographic restenosis was observed in 23% (6/26) of patients who had not had restenosis at 6 months and a reduction in minimal lumen diameter was also observed. However, in patients ($n = 20$) with maintained patency of irradiated segment at 2-year follow-up angiogram, there was no significant change in the minimal lumen diameter between 6 months and 2 years. Therefore, excluding the patients with late restenosis at 2-year follow-up angiogram, irradiated vessel segments between 6 months and 2 years remained stable.

The previous studies demonstrated that the geographic miss was strongly associated with the development of 6-month restenosis at the edge of irradiation segment [20,21]. However, the effect of geographic miss on late catch-up has not been evaluated. Although in this study, all of 6 patients with late restenosis at 2-year follow-up angiogram had geographic miss at the time of index procedure, the location of the late restenosis at 2-year follow-up was not associated with geographic miss. Therefore, geographic miss appeared not to be associated with late edge restenosis in this study. However, the larger study needs to be required for evaluation of effect of geographic miss on late edge restenosis.

A small number of patients were included in our study, but our serial angiographic follow-up findings may still represent the natural history of radiation therapy. The significant reduction in minimal lumen diameter between 6 months and 2 years might imply that restenosis developed slowly by neointima formation after radiation, which is different from that observed in bare stent implantation in de novo coronary lesion [22]. However, even if six patients (23%) was included who exhibited diameter stenosis greater than 50% at the 2-year follow-up angiogram, the target lesion revascularization rate for the entire cohort was 12% (6/50) during follow-up, which suggests that rotational atherectomy followed by beta-radiation therapy is a valuable therapeutic option for treatment of diffuse ISR.

The potential long-term adverse effects of brachytherapy on the coronary artery may be aneurysm formation and late thrombosis. In the present study, late angiographic aneurysm formation was not observed, but we did find two late total occlusions at 2-year follow-up study. Late total occlusion represents either progressive lesion obstruction or thrombosis. Thrombosis may manifest as acute coronary syndrome, but the patients in this group did not have clinical symptoms or angina of acute coronary syndrome, which suggests either silent myocardial infarction or progressive lesion obstruction. Late thrombotic occlusion can be prevented with prolonged antiplatelet therapy. In this study, aspirin and cilostazol were administered indefinitely. However, the optimal duration of antiplatelet therapy remains to be determined.

In conclusion, the late catch-up phenomenon might occur between 6 and 24 months after beta-radiation. However, the clinical benefits of rotational atherectomy followed by beta-irradiation using a ^{188}Re-MAG$_3$-filled balloon for diffuse ISR appear to be maintained at 2 years.

Study limitation need to be addressed. First, this study included a relatively small number of patients and there was no control group. Second, Two-year angiographic follow-up could be done in only 58% of patients, which may not represent true restenosis rate at 2 years. Third, this study was performed with beta-radiation using a ^{188}Re-MAG$_3$-filled balloon. Thus, the results of the present study cannot be directly compared to those of the other studies using different kinds of radiation sources, delivery methods, and interventional device.

Acknowledgements

This work was supported by grant no. 1999-2-206-001-3 from the Interdisciplinary Research Program of the KOSEF and the Cardiovascular Research Foundation, Seoul, Korea.

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