Five-Year Follow-Up After Intracoronary Gamma Radiation Therapy for In-Stent Restenosis

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Background—The Washington Radiation for In-Stent Restenosis Trial is a double-blinded randomized study evaluating the effects of intracoronary radiation therapy (IRT) in patients with in-stent restenosis (ISR).

Methods and Results—One hundred thirty patients with ISR (100 native coronary and 30 vein grafts) underwent percutaneous transluminal coronary angioplasty, laser ablation, rotational atherectomy, or additional stenting (36% of lesions). Patients were randomized to either 192-Iridium IRT or placebo, with a prescribed dose of 15 Gy to a 2-mm radial distance from the center of the source. Angiographic restenosis (27% versus 56%, P=0.002) and target vessel revascularization (26% versus 68%, P<0.001) were reduced at 6 months in patients treated with IRT. Between 6 and 60 months, patients treated with IRT compared with placebo had more target lesion revascularization (IRT, 21.6% versus placebo, 4.7%; P=0.04) and target vessel revascularization (IRT, 21.5% versus placebo, 6.1%; P=0.03). At 5 years, the major adverse cardiac event rate was significantly reduced with IRT (46.2% versus 69.2%, P=0.008).

Conclusions—In the Washington Radiation for In-Stent Restenosis Trial, patients with ISR treated with IRT using 192-Iridium had a reduction in the need for repeat target lesion and vessel revascularization at 6 months and 5 years. (Circulation. 2004;109:340-344.)

Key Words: restenosis ■ angioplasty ■ revascularization ■ radioisotopes

In-stent restenosis (ISR) after successful intracoronary stent implantation has become a major clinical problem.1,2 The recurrence rate after treatment for ISR remains high (>30%) and is not influenced by the device used in the interventional procedure.3–7 The predominant mechanism of ISR is neointimal tissue proliferation.8 Preclinical and clinical studies have shown efficacy of intracoronary radiation delivered by catheter-based systems after intervention in reducing ISR using γ and β emitters.9–13 The long-term impact and safety of this technology is unknown, with concerns of late thrombosis, aneurysm formation, accelerated vascular disease, and perforation.14 In the present study, we report the 5-year results of the Washington Radiation for In-Stent Restenosis Trial (WRIST), a prospective, randomized, double-blind trial examining the effectiveness and safety of intracoronary catheter–based radiation therapy compared with placebo as an alternative for patients requiring treatment for ISR.

Methods

The WRIST clinical trial and the follow-up of patients for up to 5 years was conducted under an Investigational Device Exemption granted by the Food and Drug Administration and approved by the Institutional Review Board and the Radiation Safety Committee at the Washington Hospital Center. The study was monitored by an independent data and safety-monitoring board, which met at 1, 3, 6, and 12 months after the initiation of the study. Informed consent was obtained from all patients before study enrollment. An independent clinical events committee reviewed and adjudicated all the clinical events that occurred in patients enrolled in the study.

Selection of Patients

The WRIST study has been previously reported.15 The study population consisted of 130 consecutive patients, 30 to 80 years of age, with previous intracoronary stent implantation in native coronary (n=100) or in aortocoronary venous bypass grafts (n=30). Patients presented with symptoms of angina and angiographic evidence of ISR. Angiographic entry criteria included diameter stenosis 50% within the stent treatment site in vessels that were 3.0 to 5.0 mm in diameter and had a lesion length <47 mm in patients who underwent successful (<30% residual stenosis without complications) angioplasty with the use of (alone or in combination) balloons, ablative devices, or additional stents. Main exclusion criteria were patients with recent (<72-hour) acute myocardial infarction (MI), ejection fraction <20%, prior irradiation treatment to the chest, evidence of angiographic thrombus, and multiple lesions in the same vessel.

Study Protocol

Before the coronary intervention, an angiogram and an intravascular ultrasound study (3.2F catheter with motorized pullback at 0.5 mm/s, Cardiovascular Imaging Systems) were performed to determine
lesion length and vessel size. Focal lesions (<10 mm length) were treated with balloon dilatation, and diffuse lesions (≥10 mm length) underwent initial ablation with use of either an excimer laser or rotational atherectomy, which was then followed by balloon dilatation. Restenting was used to optimize final angiographic results or to treat edge dissections.

At the time of radiation treatment, the patient was sedated, and the activated clotting time was maintained at >300 seconds with intravenous heparin. A closed end-lumen radiation delivery catheter was inserted into the vessel and positioned to span the lesion length. The patient was randomly assigned to receive a nylon ribbon (0.0030 inches in diameter) containing different seed trains of either placebo or 192-Ir (Best Medical International). The radiation oncologist hand-loaded the ribbon from a lead container positioned on a cart next to the table into the closed end-lumen catheter. The cardiologist documented accurate positioning of the source (by angiography) to cover the entire lesion site plus at least a 4-mm overlap of normal segments on each end. All catheterization laboratory personnel left the room during the dwell period for active source radiation or placebo treatment, except for the radiation safety officer, who measured exposure rates at various locations.

At the end of the treatment, the radiation oncologist entered the room and retrieved the ribbon into the shielded lead container, and the medical personnel returned once the radiation exposure reached background values. A final angiogram and an intravascular ultrasound study were performed. If significant reduction in luminal dimensions was observed, additional balloon dilatation or stent implantation was used to obtain optimal final results. Patients received routine postangioplasty care, including treatment with ticlopidine (250 mg orally, twice daily for 1 month), regardless of whether additional stents were implanted.

Radiation Details and Dosimetry

The prescribed dose was 15 Gy to a distance of 2.0 mm from the surface of the source for vessels between 3.0 and 4.0 mm or 15 Gy to a distance of 2.4 mm for vessels >4.0 mm in diameter. Different trains of seeds were used (5, 9, or 13 to cover total lengths of 19, 36, and 51 mm, respectively). All seeds were equal in length (3 mm separated with a 1-mm space), with a mean specific activity of 25.3–3.5 mCi. Monte Carlo calculations detected average maximum dose to the near wall of 45 Gy, whereas the average minimum dose to the far wall was 7.3 Gy.

End Points and Follow-Up

The primary clinical end point was the composite outcome of death, MI, and target lesion revascularization (TLR) at 6 months. Important secondary angiographic end points at 6 months were restenosis (defined as diameter stenosis ≥50%) and late lumen diameter loss. All patients had clinical follow-up evaluations at 1, 3, 6, 12, 24, 36, 48, and 60 months after the procedure. At 6 months, repeat coronary angiography and intravascular ultrasound studies were performed. The specific focus of this study was clinical outcomes at 5 years.

Angiographic Analysis

Quantitative coronary angiographic analysis was performed independently by 2 core angiographic laboratories blinded to the treatment assignment (Thoraxcenter and Washington Hospital Center). Angiographic binary restenosis at follow-up (angiograms 4 to 8 months after treatment) was defined as 50% diameter narrowing within the stent and in the segment including the stent plus its edges (within 5 mm). Late loss (in millimeters) was defined as the change in stent minimal luminal diameter from the final to the follow-up angiogram.

Definitions

Death was defined as all-cause mortality. Q- and non–Q-wave MI were defined as a total creatine kinase (CK) elevation ≥2 times normal or CK-MB ≥20 ng/mL with or without new pathological Q-waves in 2 or more contiguous leads. TLR and target vessel revascularization were characterized by repeat percutaneous or surgical intervention of the treated vessel. Major adverse cardiac events (MACE) were defined as death, Q-wave MI, or TLR, and late thrombosis was defined as angiographic total occlusion of the target lesion >30 days after intervention associated with a clinical event.

Statistical Analysis

The target sample size of 130 patients (with previous stent implantation in 100 native coronaries and 30 saphenous vein grafts with separate randomization) was determined (80% power and 95% CI) to demonstrate a 50% reduction in the composite clinical end point at 6 months. Data were recorded prospectively and forwarded to the data-coordinating center at the Washington Hospital Center. All clinical events were independently adjudicated by an external committee that reviewed source-documented data in a blinded fashion. Results are expressed as mean±SD. The Student’s t test was used to compare continuous variables; the χ² or Fisher’s exact test was used to compare categorical values. The composite clinical end point (TLR or MACE) was analyzed by use of Kaplan-Meier survival curves, with differences between the 2 treatment groups compared by the log-rank test. Multiple logistic regression was performed to identify variables associated with freedom from MACE at 5 years. P<0.05 was considered significant.

Results

One hundred thirty patients with ISR were enrolled in the WRIST study. Baseline clinical and angiographic characteristics of the treatment groups are shown (Table 1). Overall,
48% had diabetes, 60% had previous treatment of ISR, and 75% had a diffuse pattern of ISR (lesion length >10 mm), with a mean lesion length of 28.8±12.4 mm. Balloon angioplasty alone was used in only 14 (10.7%) lesions. Atheroablative devices were most frequently used: rotational atherectomy in 60% of native coronaries and excimer laser in 90% of vein grafts. Restenting was performed in 46 (35.4%) lesions because of either tissue prolapse (in 26 lesions) or the necessity to cover edge dissections (in the remaining 20 lesions). The mean radiation seed length was comparable in irradiated (43.0±10.2 mm) and placebo (41.4±11.4 mm, P<0.001) groups. The dwell time was 22.6±6.7 minutes to deliver the prescribed dose in irradiated patients.

All procedures were free of major adverse events, and only 2 patients required vascular access site repair. There were no deaths, subacute closure, or Q-wave MIs in hospital or after 30 days. CK-MB elevation >2 times baseline was detected in 11% of the irradiated group versus 8% of the placebo group (P=NS).

Angiographic Results
Radiation therapy at 6-month angiographic follow-up, compared with placebo, resulted in a significant reduction in restenosis both within the stent (19% versus 58%, P<0.001) and in the segment including the stent edges (26% versus 67%, P<0.001). Irradiated patients had significantly less late loss than controls (0.41±0.73 versus 0.84±0.70 mm, P=0.002). The predominant angiographic pattern of restenosis in the irradiated group was at the edges, with a mean lesion length of 10±3.1 mm, compared with a diffuse pattern of recurrence in the placebo group, with a mean lesion length of 21±10.2 mm (P=0.005). There was no evidence of perforation or aneurysm formation in the irradiated group.

Late Clinical Events
Clinical follow-up at 6 and 60 months was obtained in all patients (Table 2). An explanation for the slight difference in the TLR and angiographic restenosis rate may be based on the low threshold of operators to perform PCI based on ocular restenotic reflex and not quantitative coronary angiography. There were no differences in rates of death, Q-wave MI, or non-Q-wave MI at any time interval. At 6 months, irradiated patients had a 77% reduction in TLR compared with controls (14% versus 62%, P<0.001). Between 6 and 60 months, irradiated patients had higher TLR (21.6% versus 4.7%, P=0.04), target vessel revascularization (21.5% versus 6.1% P=0.03), and composite MACE (27.7% versus 6.1% P=0.001) compared with controls. Event-free survival (freedom from death, MI, and repeat TLR) at 5-year follow-up reflects sustainable efficacy of radiation therapy (Figure 1). Multiple logistic regression analysis indicated that radiation therapy (OR, 0.39; 95% CI, 0.18 to 0.82; P=0.001) and preminimal luminal diameter (OR, 0.32; 95% CI, 0.13 to 0.81; P=0.02) were the only predictors of freedom from MACE at 5 years. During the course of the follow-up, none of the patients developed new malignant disease, and none of the patients experienced an angiographic adverse event such as aneurysm or perforation.

Late Thrombosis
At 6 months, the late thrombosis rate was 7.7% in the irradiated group versus 3.1% in the placebo group, whereas at
24 months, the cumulative rate of late thrombosis in the radiation arm rose to 12.3% versus 6.2% in the placebo arm. Two of the documented late thrombotic events resulted in death. There was no additional evidence of late thrombosis in the radiation arm between 24 and 60 months (Figure 2).

Discussion
The present study demonstrates that intracoronary γ radiation, as adjunctive therapy to percutaneous coronary intervention for the treatment of in-stent restenosis, has declined in efficacy over 5 years compared with placebo. The dramatic reduction of radiation therapy (>60%) in clinical restenosis and the need for repeat revascularization at 6 months declined primarily between 6 and 24 months and resulted in a modest reduction of clinical restenosis at 5 years.

An important observation is the increase in the revascularization rate between 6 and 60 months, primarily in the irradiated group, which ultimately minimizes the clinical benefit observed in the irradiated group versus placebo. These findings suggest that radiation may delay in part the biological processes and that a late catch-up phenomena or late thrombosis will reduce the long-term benefit of radiation. A later occurrence of restenosis may be produced by the radiation therapy. The phenomenon of late catch-up was also reported in the Scripps Coronary Radiation to Inhibit Proliferation Post Stenting (SCRIPPS) study, when the angiographic analysis trial at 3 years showed a reduction of the minimal luminal diameter in irradiated patients (not seen in the placebo group).

It is possible that radiation therapy, with the doses used in the WRIST study, delays the restenotic biological process, which is reestablished beyond 6 months. This time interval remains to be defined and could be dose-related.

Another important observation is the increase in the late thrombosis seen primarily in the radiation group. This increase was not linear and was not seen beyond 2 years from the index procedure. Two of the deaths could clearly be related to late thrombosis. It is possible that other deaths were caused by undocumented thrombus.

The current recommendation of antiplatelet therapy after vascular brachytherapy is between 6 and 12 months. This is based on the results from the WRIST PLUS and WRIST 12 studies. However, in the WRIST study, patients were discharged with only 1 month of antiplatelet therapy recommended. This may be an explanation of the high rate of late thrombosis, ranging from 3 to 24 months after the radiation treatment. The phenomenon of late thrombosis was attributed to delay in reendothelialization of irradiated vessels and was demonstrated in the animal studies. Interestingly, there were no additional late-thrombosis events in this study or in the literature beyond 24 months. This may suggest that complete healing and reendothelialization is established at this time point, and perhaps 24 months of clopidogrel may be safer for patients undergoing vascular brachytherapy treatment.

Persistent long-term efficacy of radiation therapy is consistent with other studies. Target lesion revascularization was significantly lower at 3 and 5 years in 192-Iridium patients compared with placebo.

Caution should be observed concerning the potential risk of late effects of radiation, which may occur 10 years after treatment, as previously reported with the use of external radiation. Ongoing follow-up is imperative to assess for coronary aneurysms, perforation, accelerated atherosclerosis, or new malignancy, which are potential adverse effects related to the radiation therapy.

Conclusion
In the original WRIST, radiation therapy for patients with ISR using a 192-Iridium system is associated with a reduction in the need for repeat target lesion and target vessel revascularization at 6 months. Despite increases in late recurrences in the irradiated group between 6 and 60 months, the clinical benefit of γ radiation for this cohort remains statistically significant at 5 years. The encouraging results from the clinical trials have established intracoronary radiation as a standard of care for patients with ISR.

References


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