Repeat Intracoronary Radiation for Recurrent In-Stent Restenosis in Patients Who Failed Intracoronary Radiation

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Background—Intracoronary radiation therapy (IRT) is the only proven treatment for in-stent restenosis (ISR). It is, however, associated with a significant failure rate. The present study evaluated the outcomes of patients who underwent repeat intracoronary radiation for recurrent ISR.

Methods and Results—Fifty-one consecutive patients who failed a previous radiation treatment, presented with angina and angiographic evidence of ISR, and were treated with percutaneous coronary intervention (PCI) and repeat radiation to the same segment were studied. Twenty-five patients were treated with gamma radiation in a dose of 15 Gy, and 26 were treated with beta radiation doses of 18.3 to 23 Gy. The mean cumulative dose for this cohort was $39.5 \pm 11.9$ Gy (range, 29 to 75.6 Gy). The outcomes of those patients were compared with outcomes of 299 patients who also failed initial radiation but were treated with repeat conventional PCI to a previously irradiated segment without repeat radiation. At 9 months after treatment, the repeat-IRT group had lower rates of target lesion revascularization (23.5% versus 54.6%; $P<0.001$) and major adverse cardiac events, including target vessel revascularization (29.4% versus 61.3%; $P<0.001$). At 9 months, patients with repeat IRT were free of angiographic and clinical events related to the radiation therapy.

Conclusions—Repeat gamma or beta radiation to treat failed IRT for ISR after conventional PCI is safe and effective at 9 months and should be considered as a therapeutic option for this difficult patient subset. (Circulation. 2003;108:654-656.)

Key Words: radioisotopes n restenosis n stents

Intracoronary radiation therapy (IRT) for in-stent restenosis (ISR) in native coronary arteries and saphenous vein grafts has substantially reduced the rate of recurrent restenosis compared with conventional percutaneous coronary intervention (PCI).1-5 However, 20% to 25% of patients treated with IRT require repeat revascularization to the irradiated site because of stenosis recurrence.6,7 The optimal treatment strategy for these patients remains unclear. Repeat conventional PCI has been shown to be safe but is associated with a high recurrence rate.7 Although coronary artery bypass grafting may offer a more definitive treatment option, patients may not always be suitable for a repeat surgery that may be associated with high morbidity and mortality rates. The objective of the present retrospective registry was to examine the safety and clinical outcome of patients who received repeat IRT to a previously irradiated site after PCI for recurrent ISR.

Methods

Study Population

Retrospective analysis was performed on 350 consecutive patients from the Washington Hospital Center who (1) were previously enrolled in a brachytherapy trial or had undergone commercial IRT between July 1997 and August 2002, (2) presented with recurrence of ISR within the irradiated segment, and (3) were treated with either conventional PCI (n=299) or conventional PCI with repeat radiation (n=51).

Criteria for repeat radiation, including absence of thrombus and a minimum of 6 months between the first and second doses of IRT, were set in July 2000 for all patients who presented with recurrence of ISR after IRT. Device and radiation system were selected at the discretion of the operator. After an adequate angiographic result was obtained, patients were treated with either

1. gamma radiation ($^{192}$Ir) delivered by the Checkmate system (Cordis) in a prescribed dose of 15 Gy at 2 mm from the center of the source (n=21, 41.2%), or

2. beta radiation ($^{90}$Sr/Y) delivered by either

(a) the BetaCath system (Novoste) in a dose of 18 Gy (n=5, 9.8%) or 23 Gy at 2 mm (n=13, 25.5%), or

(b) the Galileo system (Guidant) in a P-32 emitter dose of 20 Gy at 1 mm beyond the balloon surface (n=12, 23.5%).

Manual stepping was not performed with any of the radiation devices. The mean cumulative dose (sum of the two doses) was $39.5\pm11.9$ Gy (range, 29 to 75.6 Gy).

All patients were treated with aspirin and clopidogrel before the procedure. During the intervention, heparin was administered to
maintain an activated clotting time between 250 to 300 seconds. At discharge, patients with repeat IRT were instructed to continue clopidogrel 75 mg/d for a minimum of 12 months.

Clinical Follow-Up

Patients were followed up clinically by telephone contact or office visit. Repeat angiography was available for 28 patients from the repeat-IRT group. Clinical events (target lesion revascularization [TLR], defined as the lesion segment with <5 mm margins from each end; target vessel revascularization [TVR], defined as any intervention to the treated vessel; and major adverse cardiac events [MACE], defined as composite of death, Q-wave myocardial infarction [MI], or TVR) were recorded at 9 months after treatment.

Statistical Analysis

The results are reported as the mean±SD for continuous variables and as percentages for categorical variables. Student’s t test was used to compare continuous variables, and the χ² test or Fisher’s exact test was used to compare categorical variables. A probability value of <0.05 was considered to indicate statistical significance. All reported probability values are two-sided.

Results

Of 350 patients who failed IRT for ISR and presented with recurrent anginal symptoms and documented angiographic restenosis, 51 underwent repeat PCI and IRT to the same site, whereas 299 patients were treated with conventional PCI alone. The two groups had similar baseline characteristics, except for the presence of a greater number of current smokers in the PCI-alone group (Table 1). The mean time interval from the first to the second dose of IRT was 12.6±8.1 months, and 26 of the 51 patients had a conventional PCI procedure between the two radiation treatments. In-hospital events in the repeat-radiation group were non–Q-wave MI (n=1) and pulmonary edema (n=1). Nine-month clinical follow-up was available for 100% of the repeat-IRT group and 80% of the conventional PCI group.

At 9 months, the overall rates of MACE and TLR were lower in the repeat-IRT group compared with the PCI-alone group (25.5% versus 58.4% [P<0.001] and 23.5% versus 54.6% [P<0.001], respectively) (Table 2).

There was a trend toward higher (12% to 20%) mean second and cumulative doses in the patients without MACE: 24.0±11.1 and 40.9±12.9 Gy compared with 19.2±5.6 and 36.1±7.8 Gy for patients with MACE (P=0.16 and P=0.19, respectively). There was no difference in outcome between patients treated with beta and patients treated with gamma sources. Angiographic follow-up was available in 41 patients who underwent repeat radiation at 7.6±4.9 months. None had signs of aneurysm formation or any other angiographic complications. The angiographic pattern in the patients who had a TVR event demonstrated: focal ISR within the stent (n=4), diffuse ISR (n=1), total occlusion (n=4), edge restenosis (n=2), and progression of disease (n=3). The rates of total occlusion at 9 months after the intervention were similar in the PCI+IRT group and the PCI-alone group (7.8% versus 11.8%; P=0.42).

TABLE 1. Clinical Characteristics at Time of Repeat Intervention

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Irradiated Group (n=51)</th>
<th>PCI-Alone Group (n=299)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>58.8</td>
<td>68.0</td>
<td>0.199</td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>64.59±11.3</td>
<td>60.42±10.9</td>
<td>0.057</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>40.0</td>
<td>39.6</td>
<td>0.957</td>
</tr>
<tr>
<td>Hypertension</td>
<td>87.5</td>
<td>76.0</td>
<td>0.076</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.0</td>
<td>11.3</td>
<td>0.011</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>41.2</td>
<td>50.7</td>
<td>0.210</td>
</tr>
<tr>
<td>Renal disease (creatinne &gt;2.0)</td>
<td>0.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>History of MI</td>
<td>49.0</td>
<td>58.0</td>
<td>0.231</td>
</tr>
<tr>
<td>History of cerebrovascular accident</td>
<td>15.7</td>
<td>11.1</td>
<td>0.265</td>
</tr>
<tr>
<td>Prior coronary artery bypass grafting</td>
<td>60.0</td>
<td>59.2</td>
<td>0.923</td>
</tr>
<tr>
<td>Stable angina</td>
<td>14.3</td>
<td>14.7</td>
<td>0.942</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>85.7</td>
<td>85.3</td>
<td>0.942</td>
</tr>
<tr>
<td>Canadian Cardiovascular Society class III or IV</td>
<td>77.1</td>
<td>82.5</td>
<td>0.367</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %, mean±SD</td>
<td>47±11</td>
<td>49±11</td>
<td>0.265</td>
</tr>
</tbody>
</table>

Values are given as percent of patients, with the exceptions of age and left ventricular ejection fraction, which are given as mean±SD.

TABLE 2. MACE Rates 9 Months After Repeat Intervention

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Irradiated Group</th>
<th>PCI-Alone Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE (death, Q-wave MI, TVR)</td>
<td>29.4</td>
<td>61.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR MACE</td>
<td>25.5</td>
<td>58.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>2.0</td>
<td>5.0</td>
<td>0.48</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>0</td>
<td>2.1</td>
<td>0.59</td>
</tr>
<tr>
<td>Non–Q-wave MI</td>
<td>3.9</td>
<td>5.0</td>
<td>0.73</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>TVR</td>
<td>27.5</td>
<td>57.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TLR</td>
<td>23.5</td>
<td>54.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>7.8</td>
<td>11.8</td>
<td>0.42</td>
</tr>
</tbody>
</table>

MACE rates are given as percent of patients.
Discussion
This is the first registry to report the 9-month outcomes of patients with ISR who underwent repeat IRT to the same site. This study demonstrates that repeat IRT was safe and effective at 9 months when compared with outcomes of patients who also failed initial IRT but were treated with conventional PCI alone.

Whether to use repeat IRT for patients with ISR who failed radiation previously is a dilemma involving safety and efficacy issues. Safety concerns include the vessel’s tolerance for additional radiation doses, the potential for late effects, and the allowance of adequate time for healing between the two doses.

Given the aggressive restenotic process in patients who failed IRT, a TLR of 23.5% is an acceptable outcome. These rates are slightly higher than those reported at 6 months with the initial radiation trials but are significantly lower than the TLR rates after conventional PCI without IRT for patients who failed radiation therapy (33.3% to 55.0%). They are also lower in comparison with the patients from the control group of the radiation trials for ISR, who have been reported to have TLR rates of 41% to 63%.1–5,8

It is possible that the main cause for failure of the first IRT is related to an inadequate dose because most of the patients in the early phase of the IRT trials received a dose of 14 to 15 Gy. Other potential causes are resistance to radiation, thrombosis, and edge effect.

The key questions to ask are: What is the optimal dose for repeat radiation therapy? Will higher doses be required to obtain better results for these patients? In the Long WRIST (Washington Radiation for In-Stent restenosis Trial) High-Dose studies, an increase of 3 Gy in the dose was associated with significant reduction of TLR and MACE rates in a difficult subset of patients with diffuse, long (>30 mm) ISR lesions.8 Although the dose for the failure group in the present study was similar to the initial dose for the majority of the patients, it is appealing to prescribe slightly higher doses for repeat radiation, especially in patients who present with recurrence of neointima at the treated segment. In the present study, patients without MACE at 9 months received a 15% higher cumulative dose than those who presented with MACE.

The tolerance of coronary arteries to a second dose of radiation is unknown. Doses in the range of 19 to 55 Gy, which have been administered previously in a single application, have been reported to be associated with the appearance of aneurysm formation.9 The mean cumulative dose for the present cohort was 39.5 ± 11.8 Gy. However, by fractionating the dose with an interval of ≥6 months, larger doses of IRT can be delivered more safely because time is given for repair between the two radiation treatments.10 Repeat doses of radiation are often administered to cancer patients without complications. Nevertheless, care must be taken in selecting patients and ascertaining the cause of the failure (ie, intimal hyperplasia and not thrombosis). In the present study, repeat radiation was not associated with episodes of subacute or late thrombosis, and the rate of late total occlusions was similar to that of the PCI-alone group. Although the repeat radiation patients were discharged with a minimum of 12 months of clopidogrel, it is possible that a longer duration of antiplatelet therapy will be accepted to prevent late thrombosis.8 Because the outcome of the patients was not influenced by the emitter selection, we recommend using beta emitters for repeat IRT to minimize radiation exposure to adjacent segments.

The introduction of drug-eluting stents has decreased but not eliminated ISR.11 Although IRT is currently used as the standard of care for ISR, treatment with drug-eluting stents for the same indication has yet to be proven as an effective alternative.12 Meanwhile, reports of late thrombosis for patients who failed IRT and were treated with drug-eluting stents are worrisome and warrant further caution before recommendation for patients who fail IRT.12

The present study’s limitations are the small number of subjects, the lack of randomization to a control group, and the limited angiographic and clinical follow-up (because late effects of radiation may be seen years after the therapy). Nevertheless, the results are encouraging and suggest short-term (9-month) safety and efficacy of repeat IRT for this complicated cohort.

References
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