Available online http://cvm.controlled-trials.com/content/2/1/016

Commentary

The Proliferation REduction with Vascular ENergy Trial (PREVENT)

Albert E Raizner and Grzegorz L Kaluza

The Methodist DeBakey Heart Center and Baylor College of Medicine, Houston, Texas, USA

Correspondence: Albert E Raizner, MD, Cardiac Catheterization Laboratories, The Methodist DeBakey Heart Center, 6535 Fannin, FB 1034, Houston, TX 77030, USA. Tel: +1 713 790 2620; fax: +1 713 790 5299; e-mail: araizner@tmh.tmc.edu

Received: 15 December 2000
Revisions requested: 8 January 2001
Revisions received: 9 January 2001
Accepted: 9 January 2001
Published: 1 February 2001

Curr Control Trials Cardiovasc Med 2001, **2**:16–19

(Print ISSN 1468-6708; Online 1468-6694)

Abstract

PREVENT was the first prospective, randomized placebo-controlled study of intracoronary beta radiotherapy with ^{32}P. A total of 105 patients with *de novo* or restenotic lesions, treated by stenting or balloon angioplasty, received 0 (control), 16, 20, or 24 Gy to a depth of 1 mm beyond the lumen surface. Rates of restenosis (50% diameter stenosis or more) were significantly lower in radiotherapy patients at the target site (8% compared with 39%, $P = 0.012$) and at the target site plus adjacent segments (22% compared with 50%, $P = 0.018$). Stenosis adjacent to the target site and late thrombotic events reduced the overall clinical benefit of radiotherapy.

Keywords: angioplasty, beta radiation, coronary artery disease, restenosis, stents

Introduction

Radiation therapy with sources emitting gamma and beta radiation has shown the ability to inhibit restenosis after percutaneous coronary interventions [1]. Human trials with endovascular gamma radiation demonstrated decreased restenosis in patients with prior restenosis undergoing repeat coronary angioplasty followed by radiotherapy [2,3]. Non-randomized pilot studies with endovascular beta radiation after balloon angioplasty showed a low late lumen loss and a low restenosis rate in patients with *de novo* lesions [4] as well as with in-stent restenosis [5]. PREVENT (Proliferation REduction with Vascular ENergy Trial) was the first randomized placebo-controlled trial of intracoronary beta radiation for the prevention of coronary restenosis [6].

Trial design and results

The primary objective of this study was to demonstrate the safety and performance of an intracoronary beta-radiation therapy system (Guidant Vascular Intervention, Houston, Texas). Secondary objectives included the evaluation of the effectiveness of intravascular beta radiotherapy after stent implantation (for the first time) in comparison with balloon angioplasty alone, and the relative effectiveness of three radiotherapy doses (16, 20 and 24 Gy beyond the lumen surface) in comparison with a sham radiation procedure (placebo). Radiotherapy was applied to restenotic as well as *de novo* lesions shorter than 15 mm, with a maximal total treatment length (balloon or stent) of 22 mm or less and a reference vessel diameter of between 2.4 and 3.7 mm inclusive. The intravascular radiation therapy system, the dosimetry and the procedure have been described previously in detail [6,7]. The system consists of three components: the 27 mm ^{32}P source wire, the centering spiral balloon catheter, and the automated source delivery unit. All patients received aspirin (325 mg) for the duration of the study, and ticlopidine (250 mg bid) for 4 weeks afterwards for patients who had received a procedural stent.

BERT = Beat Energy Restenosis Trial; INHIBIT = Intimal Hyperplasia Inhibition with Beta In-stent Trial; MACE = major adverse clinical event; MI = myocardial infarction; PREVENT = Proliferation Reduction with Vascular Energy Trial; QCA = quantitative coronary analysis; TLR = target lesion revascularization; TVR = target vessel revascularization.

A total of 105 patients had a successful procedure. Patients were randomized to one of four radiation treatment groups: 0 (placebo, $n = 25$), 16 Gy ($n = 26$), 20 Gy ($n = 27$), or 24 Gy ($n = 27$) to 1 mm beyond the lumen surface. Only the radiation oncologist, medical physicist, and the radiation safety officer were not blinded to treatment assignment. Clinical follow-up was obtained at 1, 3, and 6 months. Angiographic follow-up was mandated after 6 months.

The randomization was unbalanced (3:1) to detect any safety issues that would occur with radiation at a high frequency. Binary incidence rates, angiographic restenosis, target-related revascularization or failure, or combined nonspecific late ischemic end points were tested with χ^2 or exact contingency table analyses. Continuous variables were compared by using Student's *t* test.

Overall, 73 (70%) were *de novo* lesions, whereas 32 (30%) were restenotic lesions, including in-stent restenosis in 24% of patients. The angioplasty procedure included the placement of one or more new stents in 64 (61%) patients.

In-hospital major adverse clinical event (MACE) occurred in one (1.3%) radiotherapy patient [non-Q-wave myocardial infarction (MI)] and one (4.0%) control patient (non-Q-wave MI) (P = ns). There were no instances of in-hospital death or post-procedure revascularization.

Long-term (12 months) MACE [death, MI and target lesion revascularization (TLR)] occurred in 13 (16%) of the radiotherapy patients and in 6 (24%) of the control patients (P = ns). If revascularization due to restenosis at any site in the target vessel is included, MACE occurred in 21 (26%) of the radiotherapy patients and in 8 (32%) of the control patients (P = ns).

The one death and all seven post-hospitalization MIs occurred in the radiotherapy group and were considered to be acute late occlusive events. Six of the seven patients with post-hospitalization MIs had received new stents at the index procedure. The incidence of composite and individual MACEs is presented in Table 1.

Table 1

Major adverse clinical events at 12 months

Event	Radiotherapy ($n = 80$)	Control ($n = 25$)	*P* value
MACE (death, MI, TLR)	13 (16%)	6 (24%)	ns
MACE (death, MI, TVR)	21 (26%)	8 (32%)	ns
Death	1 (1%)	0 (0%)	ns
MI			
Total	8 (10%)	1 (4%)	ns
Q-wave	2 (3%)	0 (0%)	
non-Q-wave	6 (7%)	1 (4%)	
TLR5 (6%)	6 (24%)	<0.05	
TVR	17 (21%)	8 (32%)	ns

MACE, major adverse clinical events; MI, myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization.

TLR was significantly lower in the radiotherapy group than in the control group. There was a trend toward a lower incidence of revascularization for restenosis at any site in the target vessel (TVR) in the radiotherapy patients. The results of the quantitative coronary analysis (QCA) are summarized in Table 2. The target site was defined as the segment of balloon and stent injury required to treat the target lesion. Adjacent segments were defined as the segments of artery outside the target site and extended to 5 mm beyond the radiation zone. QCA showed no significant differences between radiotherapy patients who received new stents and those who underwent balloon angioplasty. In addition, all three dose groups demonstrated similar decreases in angiographic restenosis indices in comparison with the control group, although the trial population was not large enough for statistically meaningful comparisons between subgroups. In patients with follow-up angiography who received 16 Gy ($n = 23$), 20 Gy ($n = 25$), and 24 Gy ($n = 25$), similarly low late lumen losses (0.12 ± 0.49, 0.31 ± 0.79, and 0.23 ± 0.48 mm, respectively) and late loss indices ($4 \pm 28\%$, $18 \pm 50\%$, and $10 \pm 25\%$, respectively) were found.

Table 2

Quantitative coronary angiographic analysis

	^{32}P group ($n = 80$)	Control ($n = 25$)	*P* value
Acute gain (mm)	1.9 ± 0.6 ($n = 80$)	1.9 ± 0.4 ($n = 25$)	ns
Late lumen loss (mm)	0.2 ± 0.6 ($n = 73$)	1.1 ± 0.7 ($n = 23$)	<0.0001
Late loss index (%)	11 ± 36 ($n = 73$)	55 ± 30 ($n = 23$)	<0.0001
Binary restenosis (>50%)			
Target site	6/73 (8%)	9/23 (39%)	0.0012
Target site plus adjacent segments	17/76 (22%)	12/24 (50%)	0.018

All values are means ± SD.

The efficacy of beta radiotherapy with ^{32}P

PREVENT was the first trial of beta radiotherapy for the prevention of restenosis to use a control group. Although it was a pilot study designed to assess the safety of beta radiotherapy with ^{32}P, valuable information was obtained about the efficacy of beta radiotherapy. In the target site there was a marked decrease in late lumen loss and late loss index. Additionally, angiographic restenosis was decreased by 79%. If one incorporates adjacent segments into the restenosis calculation, an almost equally impressive 55% decrease was achieved by radiotherapy (Table 2). Radiotherapy with ^{32}P therefore seems to be as effective as gamma radiotherapy [2,3] in reducing restenosis after angioplasty.

The study population consisted of the broad spectrum of patients undergoing percutaneous coronary intervention, including in-stent restenosis; newly placed stents were included. In patients receiving stents, radiotherapy was administered after stent placement and completion of the angioplasty procedure. This is in contrast with the Beta Energy Restenosis Trial (BERT) of beta radiotherapy with $^{90}Sr/^{90}Y$, in which stenting was performed after radiotherapy had been administered [4]. Because beta radiation is less penetrating than gamma radiation and does not penetrate stainless steel stents, a concern existed that beta radiotherapy would be ineffective when administered to stented arteries. This trial proved the contrary, indicating that beta radiotherapy with ^{32}P inhibited restenosis in stented arteries as effectively as in non-stented arteries. Quantitative coronary angiography showed no significant differences between patients who received stents ($n = 50$) and those who received balloon angioplasty ($n = 30$) in late lumen loss (0.20 ± 0.50 mm compared with 0.25 ± 0.74 mm; $P =$ ns) or in late loss index ($9 \pm 28\%$ compared with $13 \pm 46\%$; $P =$ ns). This observation allowed the initiation of the INtimal Hyperplasia Inhibition with Beta In-stent Trial (INHIBIT), a multi-center randomized control trial in patients with in-stent restenosis. In addition, the similar efficacies of three dose levels (16, 20 and 24 Gy to a 1 mm depth in the artery wall) suggested that the therapeutic window for vascular radiotherapy is not narrow.

The PREVENT trial was not designed or powered to show efficacy based on clinical endpoints. Nevertheless, TLR was significantly lower in the radiotherapy group (6% compared with 24%, $P < 0.05$) and there was a distinct trend observed in decreases in TVR (21% compared with 32%) and MACE (death, MI, TLR) of 16% compared with 24%.

Side effects of radiation

Several potential radiation-related issues were identified in this study. Despite the marked inhibition of the restenotic process at the target site that received the full beam of radiation, some patients developed narrowing at, or adjacent to, the edge of the radiation zone. Most cases of the 'edge effect' revealed evidence of balloon or stent injury that was incompletely covered by the radiotherapy treatment; a 'geographic miss'. Consequently, the strategy of incorporating a broad margin of treatment beyond the segment of balloon or stent injury should lessen or eliminate this phenomenon.

An additional observation of this investigation was the occurrence of late MI in 7 radiotherapy patients during the 12-month follow-up. It is reasonable to speculate that the cause of these late thrombotic events was the delayed formation of 'protective' neointima over the exposed stent material, thereby prolonging the potential for late stent thrombosis to occur. On the basis of this observation, a strategy of prolonged anti-platelet therapy (3–6 months) and minimizing the use of new stents in patients undergoing radiotherapy was advocated.

Operational characteristics of the Guidant system

An important goal of this study was to assess the operational characteristics of the Guidant system. The system is unique in that it incorporates a radiation delivery catheter with a spiral balloon. The spiral balloon allows side-branch and distal perfusion while centering the source. The source is delivered by an after-loader (source delivery unit) that allows hands-off operation of this radiotherapy unit, and computer algorithms that precisely calculate dosimetry and dwell times. Dwell times range from 1.0 to 9.6 minutes (mean = 4.6) and the time added to the angioplasty procedure was only 12 ± 6 minutes. Fractionation of the treatment was required in only 9% of patients.

Conclusions

In summary, PREVENT demonstrated that beta-radiotherapy with ^{32}P with an automated system and source centering was a safe and potent inhibitor of restenosis in a broad spectrum of patients undergoing percutaneous coronary intervention. Several problems were identified, including an 'edge effect' due to a 'geographic miss', and late thrombosis primarily in patients with newly implanted stents. The trial supports the further exploration of beta radiotherapy in larger-scale clinical trials of specific subsets of patients, including those with in-stent restenosis.

Acknowledgements

PREVENT was supported by Guidant Vascular Interventions, Santa Clara, California.

References

1. Kuntz RE, Baim DS: **Prevention of coronary restenosis: the evolving evidence base for radiation therapy.** *Circulation* 2000, **101**:2130–2133.
2. Teirstein PS, Massullo V, Jani S, Popma JJ, Mintz GS, Russo RJ, Schatz RA, Guarneri EM, Steuterman S, Morris NB, Leon MB, Tripuraneni P: **Catheter-based radiotherapy to inhibit restenosis after coronary stenting.** *N Engl J Med* 1997, **336**:1697–1703.

3. Waksman R, White RL, Chan RC, Bass BG, Geirlach L, Mintz GS, Satler LF, Mehran R, Serruys P, Lansky AJ, Fitzgerald P, Bhargava B, Kent KM, Pichard AD, Leon, MB: **Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis.** *Circulation* 2000, **101**:2165–2171.
4. King SB, Williams DO, Chougule P, Klein JL, Waskman R, Hilstead R, Macdonald J, Anderberg K, Crocker IR: **Endovascular beta-radiation to reduce restenosis after coronary balloon angioplasty: results of the beta energy restenosis trial (BERT).** *Circulation* 1998, **97**:2025–2030.
5. Waksman R, Bhargava B, White L, Chan RC, Mehran R, Lansky AJ, Mintz GS, Satler LF, Pichard AD, Leon MB, Kent KK: **Intracoronary beta-radiation therapy inhibits recurrence of in-stent restenosis.** *Circulation* 2000, **101**:1895–1898.
6. Raizner AE, Oesterle SN, Waksman R, Serruys PW, Colombo A, Lim YL, Yeung AC, van der Giessen WJ, Vandertie L, Chiu JK, White LR, Fitzgerald PJ, Kaluza L, Ali NM: **Inhibition of restenosis with beta-emitting radiotherapy: report of the Proliferation REduction with Vascular ENergy Trial (PREVENT).** *Circulation* 2000, **102**:951–958.
7. Raizner AE, Kaluza GL, Ali NM: **Clinical experience with a spiral balloon centering catheter for the delivery of intracoronary radiation therapy.** *Cardiovasc Radiat Med* 2000, **3**:214–219.