

Emerging Role of Endovascular Brachytherapy in Arterial Restenosis

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Abstract: Angioplasty and stenting are highly effective modalities for the treatment of occlusive arterial disease yielding excellent immediate results. However, a restenosis rate of 20% to 40% remains a cause for dissatisfaction. In an attempt to bring down the restenosis rate, radiation has been tried in different ways using external as well as endovascular radiation. Various beta and gamma emitters such as ¹⁹²Ir, ³²P, ⁹⁹P and ¹⁸⁸Re have been tried using different techniques such as remote afterloading HDR, manual remote afterloading, radioactive stents and radioactive liquid Rhenium filled balloons. Results of historical trials such as the WRIST trial (Washington Radiation for In-Stent Restenosis Trial), the SCRIPPS trial (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting), the BERT trial (beta emitter for intracoronary brachytherapy) etc. have been discussed. Although various mechanisms such as recoil, neo intimal proliferation and vascular contracture have been postulated to be involved in the process of restenosis, a better understanding of the molecular biology of restenosis and definitions of the actual targets, the timing of radiation, dose rate and fractionation etc. shall help us in achieving superior results.

Key words : *Endovascular Brachytherapy.*

Introduction

The treatment of occlusive arterial disease (coronary or peripheral) has undergone a slow evolution over past few decades. Various treatment techniques such as atherectomy, lasers, angioplasty and stent placements have been tried. Of these, angioplasties and stents have provided excellent immediate results but have been accompanied with a high rate of restenosis (30-40%) within 6-12 months. The incidence of post angioplasty restenosis varies with the anatomic site: 20% for aorto-iliac¹ and 40% for femoro-popliteal angioplasty. Similarly, the mesenteric and renal arteries have high restenosis rate.

Mechanism of Restenosis

The various mechanisms postulated to be involved in the process of restenosis are: recoil, neo intimal proliferation and vascular contracture². The causes of acute closure include spasm with or without thrombosis, dissection with complete closure and elastic recoil. Most common mechanism of delayed post angioplasty reconstruction is fibro cellular intimal hyperplasia (FIH). The major constituent of this is the smooth muscle cell (SMC). Bromo deoxy uridine labeling has shown that 10-20% of medial SMCs begin to proliferate within 24-48 hrs of balloon angioplasty. These SMCs then migrate to the intima at around 4 days, where some undergo further cycles of cell proliferation. The ongoing synthesis of connective tissue matrix and cellular hypertrophy causes progressive intimal thickening for up to 8 weeks.

The endotheloid denudation caused by balloon angioplasty results in loss of growth-inhibitory heparin-like glycosamine glycan³. Similarly, the platelets that adhere to the area of injury release anti heparin factors such as platelet factor 4 heparitinase. These reverse the effects of heparin sulphates produced normally by the smooth muscle cells. The heparin sulphates are believed to be responsible for maintaining the smooth muscle cells in a non-proliferating state⁴. This leads to actively proliferating SMCs that secrete extra cellular matrix. The endotheloid injury also results

in platelet adhesion. After adhesion, the platelets release all the contents of their alpha granules, including platelet derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor- β (TGF- β) and platelet factor EGF and TGF- β exert a synergistic effect on cellular proliferation. As a response to vascular injury and inflammation, the aggregated lymphocytes may play a role in intimal proliferation by release of their cytokines such as tumor necrosis factor, interleukins and TGF- β ⁵. It has also been seen that within hours of balloon induced injury, there is release of fibroblastic growth factor and angiotensin-II. These activate the proto-oncogene that is responsible for the transduction of mRNA in neo intimal and vascular smooth muscle cells.

Thus, a number of mechanisms collectively constitute the response to injury. When healing occurs in a controlled manner, the vessel wall is remodeled with an enlarged lumen. When the healing is uncontrolled, the hyperplastic lesion of restenosis results.

Exploring the role of vascular radiation

External Radiation : Radiation is known to be effective in the treatment of benign proliferative disorder such as keloids, heterotopic bone formation, pterygium of eye, graves exophthalmos⁶ and gynecomastia. This concept has been extended to the pathologic proliferative response after angioplasty. Various groups carried out treatment with external radiation to see the impact on restenosis. Schwartz et al⁷ tested a dose of 4 and 8Gy to stented pig coronary artery using Orthovoltage radiation and met with poor results. This was attributed to the use of Orthovoltage radiation, low dose of radiation and use of metallic stent. Styles et al⁸ used mega voltage x-rays (14Gy) immediately before, after or 2 days after the balloon injury. They found reduced neo intimal formation as compared with controls. They showed evidence of focal myocardial necrosis. To reduce the incidence of toxicity from even high doses sophisticated treatment techniques had to be evolved. The advantage of treatment with external radiation are that it can be done in a regular radiotherapy room, has the potential for fractioning the treatment course and time the treatment in

500mg for one month. Late total occlusion of the culprit lesion occurred in 12% of beta WRIST and 8% of gamma WRIST patients.

WRIST trial (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) : Teirstein et al¹⁴ have reported 100% clinical follow up with ¹⁹²Ir treated patients and have shown reduction in total lesion revascularisation by 74% at 6 months and 68% at 3 years. They reported reduction in angiographic restenosis by 69% at 6 months and 48% at 3 years. No perforation, aneurysm or pseudoaneurysm was reported.

Leon et al¹⁵ have reported results of a multicentric double blind randomized clinical trial, the gamma one trial wherein they have shown statistically significant decrease in the rate of revascularisation of the target lesion in the ¹⁹²Ir group (24.4% vs. 42.1%) as compared to the placebo and also a decrease in the rate of progression to the prespecified composite primary end point of death, Myocardial infarct (MI), emergency bypass surgery and revascularisation of target lesion in the ¹⁹²Ir group (28.2% vs. 43.8%) in the placebo group. They however pointed out an increase in the late thrombosis (5.3% vs. 0.8%) in ¹⁹²Ir vs. placebo group resulting in more late MI (9.9% vs 4.5%). This occurred in patients only after discontinuation of antiplatelet therapy and who had received new stents at the time of radiation treatment. These findings are similar to those in earlier reports from several other trials of vascular irradiation using different isotopes in which therapy with anti platelet drugs was used for only 1 to 2 months following radiation¹⁶.

BERT Trial (Beta emitter for intracoronary brachytherapy) : Spencer King et al¹⁷ have used⁹⁰ Sr/Y for intracoronary brachytherapy and reported restenosis rate of 15%. This was the first trial of endovascular brachytherapy approved by the FDA and resulted in significant decrease in the treatment time and operator exposure.

RHENIUM - 188 Trials : Park et al¹⁸ have described treatment of diffuse in stent restenosis with rotational atherectomy followed by radiotherapy with Rhenium-188 Mercaptoacetyl triglycine-filled balloon. It can be applied to coronary arteries with a large diameter as well as angulated arterial segments without the aid of a centering device. ¹⁸⁸Re is a high energy beta emitter with a maximum energy of 2.12 Mev that is available as Rhenium perhenate solution from the 188W/188Re generator (Oak Ridge National laboratory, Tennessee) and has a half life of 17 hours. Restenosis rate of 10.4% has been reported at a follow up of 5.8+1.7 months of 50 treated patients. This is encouraging considering the long length of lesion (25.5 + -12.7mm). These results were superior to those by Hoher et al¹⁹. This may be attributed to inclusion of only restenosis patients, and use of atherectomy and optimal balloon angioplasty. The advantages of this form of treatment are that it can be used for treatment of vessels of various sizes, angulated segments, uniform dose distribution and no centering device issues. No late thrombosis has been reported so far and may also be attributed to the 6-month use of aspirin and cilostazol. Figure 4 illustrates the difference in dose distribution achieved by centering versus non-centering source of radiation. Two feasibility trials the CURE trial at Columbia University and the RADIANT trial are using radioactive liquid filled balloon.

Indian trial "INDIRA" of "Intracoronary irradiation in the prevention of coronary re stenosis" is a prospective randomized trial in collaboration with the Long Beach Memorial Medical center USA and involves four major medical centers in India i.e. MediCiti Hospital, Care Hospital, Apollo Hospital and Bibi Cancer center. 800 de novo patients are to be randomized to receive 11 Gy at 3mm radius. The study was approved by the Atomic Energy

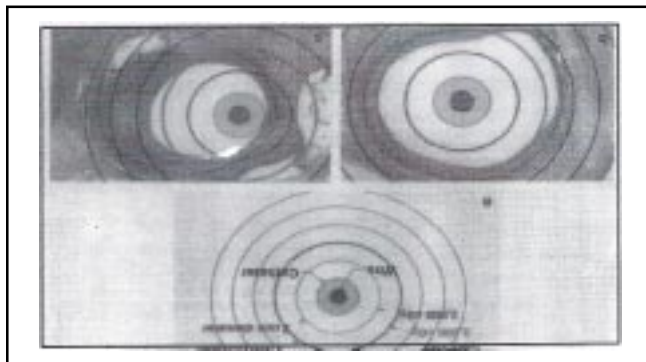


Fig.4: (a) Dose versus distance away from center of source. (b) Source centered in artery. (c) Source not centered in artery.

Regulatory Board and the trial was started in December 1998.

The European society for therapeutic radiology (ESTRO) and oncology working group²⁰ and the American association of Physicists in medicine task group on "Intravascular brachytherapy"²¹ have addressed general terms and concepts for target and dose specification as well as detailed recommendations for dose prescription, recording and reporting in Endovascular brachytherapy for both peripheral and coronary arteries. An example of prescribing, recording and reporting for a coronary artery with gamma radiation (¹⁹²Ir, non centered) as recommended by ESTRO is shown in Appendix A.

Conclusion

Endovascular Brachytherapy is still in its infancy. A better understanding of the molecular biology of restenosis and definitions of actual targets responsible for restenosis shall help us in achieving superior results with the same modality as well as help develop newer concepts in the treatment.

Issues such as the timing of radiation, length of the segment to be treated, dose, fractionation, dose rate and the point of prescription are still investigational and are being addressed to in various clinical trials. Prevention of late thrombosis following vascular brachytherapy needs to be looked at. A close collaboration between the interventional cardiologists, radiobiologists, radio oncologists, medical physicists and the industry is required.

Appendix A

Clinical Situation : 59-year-old female with a history of coronary disease for 2 years. Twenty-four months ago stenting of LAD was performed. Control angiography showed in-stent restenosis.

Aim of Therapy : Angioplasty of in-stent restenosis to establish normal arterial patency and endovascular brachytherapy to prevent restenosis.

Technique : Dilatation with 30mm/3.5mm diameter PTCA balloon and brachytherapy using 4F diameter non-centered radiation delivery catheter with ¹⁹²Ir ribbon source (14 seeds, 55mm). Following GRANITE, GAMMA 2 protocol with modifications.

Description of source, devices and technique

Isotope: ¹⁹²Ir, encapsulated in stainless steel. Source type : Source ribbon, 14 seeds (each seed 3x0.5mm, 1mm spacing), 55mm

length. Source strength: Reference air kerma rate of 0.133 cGy/h @ 1m, 854.4MBq (23.09mCi) per seed, 65.1cGy/min at 2mm from the source axis. Source movement: None Delivery device : Manual afterloader (Cordis Checkmate IRT (TM) System). Delivery catheter: 4F non-centered catheter.

Recording and reporting lengths, depths and dose

Lesion Length: 12mm; Interventional Length: 30mm; Clinical Target Length/Planning Target length: 40mm ASL:35mm; Reference Isodose Length: 46mm; Reference Lumen Diameter: 3.4mm; Reference Depth: 1.0mm

Dose prescription

Prercription point: 2mm from the source axis; Dose and dose rate: 14Gy, 0.65 Gy/min.

Dose recording and reporting

Reference Depth Dose (2.7mm) - 9.5Gy; Reference Lumen Dose (1.7mm) - 18.2 Gy; Minimum and maximum values for non-centered device: Reference Depth Dose min/max-6.4/19.5Gy; Reference Lumen Dose min/max-9.7/100Gy.

Time dose pattern

Total Treatment Time: 21.5 min

Total Reference Air Kerma: 0.048cGy@1m

References

1. Kumpe, D.A.; Becker, G.J. Percutaneous transluminal angioplasty and other endovascular technologies, 4th Ed. In: Rutherford, R.B., ed. Vascular surgery. Philadelphia: WB Saunders; 1995;352-394.
2. Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong C, Honk MK, Kovach JA, Leon MB. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996;94:35-43.
3. Castellot, J.J.; Addonizio M.L.; Rosenberg, R.; Karnovsky, M.J. Cultured endothelial cells produce a heparin-like inhibitor of smooth muscle cell growth. *J. Cell. Biol.* 1981;90:372-377.
4. Campbell, G.R.; Campbell, J.H. Smooth muscle phenotypic changes in the arterial wall homeostasis: Implications for the pathogenesis of atherosclerosis. *Exp. Mol. Pathol* 1985;42:139-162.
5. Ip, J.H.; Fuster, V.; Israel, D.; Badimon, L.; Badimon, J.; Chesebro, J.H. The role of platelets, thrombin, and hyperplasia in restenosis after coronary angioplasty. *J Am. Coll. Cardiol.* 1991;17:77B-88B.
6. Donaldson SS, Bagshaw MA, Kriss JP. Supervoltage orbital radiotherapy for Graves' ophthalmopathy. *J Clin Endo rinol Metab.* 1973;37:276-285.
7. Schwartz RS, Koval TM, Edwards WD, et al: Effect of external beam irradiation on neointimal hyperplasia after experimental coronary artery injury. *J Am Coll Cardiol* 1992;19:1106-1113.
8. Styles T, Marijianowski MMH, Robinson KA, et al: Effects of external irradiation of the heart on the coronary artery response to balloon angioplasty injury in pigs. *Proc Adv Cardiovasc Radiat Ther* 11,1997.
9. Wiedermann JG, Marboe C, Amols H, et al: Intracoronary irradiation markedly reduces neointimal proliferation after balloon angioplasty in swine: Persistent benefit at 6-month follow-up. *J Am Coll Cardiol* 1995;25:1451-1456.
10. Waksman R, Robinson KA, Crocker IR, et al: Intracoronary radiation prior to stent implantation inhibits neointima formation in stented porcine coronary arteries. *Circulation* 1995;92:1383-1386.
11. Condado JA, Waksman R, Curdiel O, et al: Long-term angiographic and clinical outcome after Percutaneous transluminal coronary angioplasty and intracoronary radiation therapy in humans. *Circulation* 1997;96:727-732.
12. Verin V, Urban P, Popowski Y, et al: Feasibility of intracoronary β -irradiation to reduce restenosis after balloon angioplasty: A clinical pilot study. *Circulation* 1997;95:1138-1144.
13. Waksman R, Ajani AE, White RL, Pinnow E, Mehran R, Bui AB et al. Two-year follow-up after beta and gamma intracoronary radiation therapy for patients with diffuse In-stent restenosis. *Am J Cardiol.* 2001;88:425-428.
14. Teirstein PS, Massullo V, Jani S, et al. Three-year clinical and angiographic follow-up after intracoronary radiation. Results of a randomized clinical trial. *Circulation* 2000;101:360-365.
15. Leon MB, Teirstein PS, Moses JW et al. Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N Engl J Med.* 2001;344:250-256.
16. Waksman R, White RL, Chan RC, et al. Intracoronary gamma-radiation therapy after angioplasty inhibits recurrence in patients with in-stent restenosis. *Circulation* 2000;101:2165-71.
17. King III SB, Williams DO, Chougule P et al. Endovascular β -radiation to reduce restenosis after coronary balloon angioplasty results of the beta energy restenosis trial (BERT). *Circulation* 1998;97:2052-2030.
18. Park SM, Hong MK, Moon DH, Oh SJ, Lee CW, Kim JJ, Park BJ. Treatment of Diffuse In-stent restenosis with rotational atherectomy followed by radiation therapy with a rhenium-188-Mercaptoacetyltriglycine-filled balloon. *J Am Coll Cardiol,* 2001;Vol.38,No.3,631-637.
19. Hoher M, Wohrle J, Wohlfrom M, et al. Intracoronary β -irradiation with a liquid 188RE-filled balloon: six-month results from a clinical safety and feasibility study. *Circulation* 2000;101:2355-60.
20. Potter R, Limbergen EV, Dries W et al. Recommendations fo the IVA GEC ESTRO working group; prescribing, recording, and reporting in endovascular brachytherapy. Quality assurance, equipment, personnel and education. *radiother Oncol* 2001;59(3):339-360.
21. American Association of Physicist in Medicine TG n. 60. 1999 Intravascular brachytherapy physics: Report of the AAPM Radiation Therapy Committee. Task Group No. 60 *Med. Phys.* 26:119-152.

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