Radiation Therapy for Prevention and Treatment of Restenosis

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Coronary revascularization with percutaneous transluminal angioplasty (PTCA) and stenting is widely used as standard procedure in patients with coronary artery disease. More than 500,000 percutaneous coronary revascularization procedures are carried out in the US annually[1]. However, coronary restenosis is a major problem in these patients. Restenosis occurs in 30-40 percent patients of patients undergoing PTCA alone and in 20-30 percent patients undergoing coronary stenting[2]. More than 150,000 cases of restenosis occur every year in US. Investigators have tried novel therapeutic procedures to tackle with this problem. Since restenosis is essentially a cell proliferative procedure there has been efforts to find ways and means to inhibit cellular proliferation at the site of intervention. Intra-coronary radiotherapy has been proposed as possible means for preventing restenosis exploiting its cytotoxic potential.

Key Words: Radiation therapy, PTCA, Stent restenosis, isotopes

Ionizing radiation has recently generated much interest as a new treatment option for restenosis after vessel injury[3]. Two delivery methods are used for endovascular radiation. One relies on high activity γ or β sources such as ribbon, seeds, or liquid to deliver a dose of radiation locally through a catheter in a limited period of time. As these radioactive sources are positioned in the vessel lumen, sufficiently high-energetic β isotopes are required in order to reach the outer limit of the vessel. Indeed, recent evidence indicates that cell proliferation in the adventitia needs also to be controlled to limit the vessel remodeling after injury[4]. The second approach is based on a radioactive stent for long exposure and continuous low dose-rate treatment. All presently available radioactive stents are created through ion-implantation of a specific isotope (e.g. 32P) or particle-bombarded to generate isotopes from the stent structures[5,6]. External radiation therapy is also contemplated but its indications seem more oriented towards the peripheral vascular system due to the technical difficulties to treat a moving target.

Principles of radiobiology

Ionizing radiation has a number of effects on target cells, the most obvious being cell killing. For highly differentiated cells that do not divide, e.g., neurons, cell death is defined as a loss of specific function. Very high doses (>100 Gy) are required to eliminate cells in a non-proliferating system. For proliferating cells, death occurs at a much lower dose. Strong evidence indicates that the nucleus, specifically DNA, is the principal target for radiation-induce cell death. An inverse relationship exists between cell survival and the number of lethal, asymmetrical exchange type chromosome aberrations. When the cell divides, chromosomal aberrations may be severe enough to prevent the completion of division. Others cells may divide successfully and even undergo several divisions before dying due to cumulative effects of DNA damage. In addition to mitotic death, ionizing radiation may induce apoptosis[7]. As opposed to necrosis, which is accompanied by an inflammatory response, apoptosis is activated by specific signals, which initiate a cascade of biochemical and morphological events culminating in cell death without inflammation. The importance of apoptosis after ionizing radiations is largely unknown and probably remains very time limited. To date, radiation therapy in the context of restenosis has not been shown to increase apoptotic cell death[4].

Cell killing is not the only effect of ionizing radiations. It is now well established that radiation may induce early and late response gene[8]. The products of these genes, specifically growth and cytokines contribute to the overall response of the irradiated tissue. A series of growth factors that have been demonstrated to play a role in restenosis after vessel injury, have also been shown to be synthesized or released after radiation injury. These factors are clearly implicated in tissue reaction such as inflammation, repopulation, and tissue repair and fibrosis[9]. It is therefore vital to bear in mind that radiation injury shares some similarity with vessel injury after balloon angioplasty or stent implantation.

Catheters and radioactive stents deliver radiations at different dose-rates. The dose-rate is an important parameter determining the biological consequences of an absorbed dose[10,11]. As a rule in radiobiology, the biological effect of a given dose is lowered if the dose-rate is reduced and the overall exposure time increased[10]. The dose is particularly significant between 0.1Gy/h and 1Gy/min. At high dose-rate, the radio-sensitivities of normal cells show little variations while decreasing the dose-rate amplifies the differences in radiation response of cells and tissues. This is a direct consequence of DNA repair during protracted exposure. Decreasing the dose-rate or dose fractionation is usually exploited in cancer therapy to spare normal tissues and limit the delayed effects of radiation such as fibrosis.

Basics of physics and radiation protection

For the sake of clarity, ionizing radiation may be defined

as electromagnetic or particulate. Electromagnetic radiations such as γ-rays or x-rays do not differ in properties but reflect the way in which they are produced. X-rays are produced extranuclearly while γ-rays are produced intranuclearly during isotope disintegration. β-Particles has the same characteristics as electrons. When they are slowed down by nuclei interaction, β-particles give rise to X-rays called "Bremsstrhalung". This process is also used to create X-rays in a catheterization laboratory, where electrons accelerated by voltage differential are abruptly stopped by the anode to generate X-rays for imaging. It is well known that the range of penetration of X-rays and γ-rays is much greater than that of β- particles. Strict radioprotection is required with these γ-sources. Although, β-particles only penetrates a few millimeters in tissue, manipulation of β sources still requires special attention. Depending on their energy β-particles can travel a significant distance through air, and therefore, precautions are required to limit the risks of source escape. "Bremsstrahlung" is proportional to the atomic number of the interacting matter and covers the energy spectrum of the β isotope. Lead shielding commonly used to stop γ or X-rays is inappropriate for β-radioprotection and lucre or plastic protectors are also required.

The principle of radiation protection in catheterization laboratory is governed by the "As Low As Reasonably Achievable" (ALARA) principal. The manipulation of high activity γ-sources such a used in brachytherapy units, requires modifications in the working habits of the cardiac cath. lab. Most importantly, after insertion of these γ sources in a patient, the staff is usually requested to leave the room and the patient during the treatment time (about > 15min). During the manipulation of β sources, the staff does not need to leave, although the "Bremsstrahlung" created by the patient body interactions with β-particles may add somewhat to the dose (X-rays) usually received by intervention cardiologists. The manipulation of a pure β radioactive stent obviously simplifies radiation protection measures. The introduction of such radioactive sources in a regular catheterization lab is highly regulated by national radiation agencies such as the American Association of Medical Physicists, which has recently emitted guideline (Task group 60) and will continue to closely monitor this rapidly evolving field[12].

Experimental result

External Radiation

Initial experiments involving external X-rays irradiation after balloon angioplasty or stent implantation yielded negative result[3]. Recent experiments using rabbit or rat models have shown a dose-dependent benefit and suggested the importance of the timing of radiation delivery. Larger irradiated volume, however, was associated with increased adverse effects such as acute inflammatory response and fibrosis including myocardial fibrosis. It remains unclear at the present time whether this technology will ever be applicable to human coronaries although it present certain advantages such as the possibility for delayed and/or fractionated treatment in case of peripheral vessels.

Endovascular Irradiation

Several groups at Columbia University, Emory University, Baylor College of Medicine in the USA and Geneva University in Europe have pioneered the endovascular use of radioactive sources for prevention of restenosis after balloon angioplasty or before stent implantation[3]. It appears that single doses in excess of 10 Gy produced a highly significant reduction in neointima formation in all animal models tested. However, lower doses were either ineffective or even produced worse result as compared with controls. While investigators at Columbia and Emory showed a persistent benefit at 6 months, others have shown that this early benefit disappeared over time. It should also be noted that fibrosis was sometimes described in the three vessel layers. Although follow-up at 6 months was not accompanied by morphological deterioration, abnormalities in vessel vasomotion persisted.

Radioactive stents

Research groups at Heidelberg University (Germany and Isostent Inc. (USA) developed several radioactive stent prototypes which were evaluated in pig and rabbit models[3]. After showing early and late benefit with mixed γ and β isotope-bounded stents, they initiated experiments using 32P ion implanted Palmaz-Schatz stents, confirming early benefit with several activities. However, the analysis of results showed a benefit at high and very low activities while intermediate-activity stents were associated with a 400% increase in neointima formation. Moreover, recent data with ^{32}P radioactive stents implanted in atherosclerotic pig coronary arteries have not shown any benefit at 6 months. A group in Los-Angeles has also reported preliminary data demonstrating some benefit using nitinol-bombarded stents.

Clinical results

Peripheral vessels

A group in Frankfurt, Germany has now accumulated experience in treating more than 25 patients with endovascular high-dose rate ^{192}Ir source for recurrent stenosis or occlusion of stented femoral arteries[13]. With follow-up extending for more than 6 years, only 4 reocclusions were demonstrated and no adverse events were reported. Waksman at Emory University evaluated the possibility of an endovascular ^{192}Ir source to treat narrowed arterio-venous fistulas in chronic dialysis patients. In this uncontrolled population, 40% of the

vessel remained patent at 44 weeks. Nori et al. using external radiation, have reported 70% patency at 6 months for the same indication. As a preamble to the PARIS trial, Waksman has also shown the feasibility of using a ^{192}Ir source with a centering balloon to treat stenosed superficial femoral arteries.

Coronary vessels

Condado et al. from Venezuela first reported the use of endovascular ^{192}Ir to deliver 20 or 25 Gy in 21 patients after balloon angioplasty or stent implantation (table 1). Quantitative coronary analysis revealed a significant early loss at 24 hrs but almost no late loss. The restenosis rate in the twenty patent arteries was 20%. The Late Loss Index (late loss/acute gain) was reported to be 19% compared with an expected value of 25-45%, suggesting a beneficial effect on late remodeling events.

Table 1 Clinical Trials for Coronary Vessels: Catheter-Based (Adapted from http//www.radiationonline.com)

PI-indication	Name	Design	Isotope	Doses (Gy)	Comments
Condado /Angiorad		Open label, radiation post balloon angioplasty in 21 patients (22 native coronary arteries)	192_{Ir}	20&25 actual doses 19-55	Completed. Clinical and angiographic follow-up at 8 and 36 months demonstrated safety & low late loss indices
Teirstein/Best Medical	SCRIPPS	Single center double blind randomized in 55 patients with restenosis and stenting	192_{Ir}	8-<30 to media by IVUS	Completed. Reduction of restenosis in the irradiated group by clinical, IVUS and angiograms at 6 months
Waksman/CRF, WHC	WRIST (native coronaries)	Single center double blind randomized in 130 patients with in-stent restenosis	192_{Ir}	15 to 2.0 mm vessels 3-4 mm	Significant reduction in restenosis rate 67% and the need for revascularization 63%
Waksman/CRF, WHC	SVG WRIST	Multicenter double blind randomized in 120 patients with in-stent restenosis	192_{Ir}	15 to 2.4 mm for vessels >4.0mm	Initial results showed reduction in restenosis in the irradiated vein grafts
Waksman Instent restenosis, Long Lesions(36-80mm)	WRIST-Long	Single center, Double blind Randomized, n=120	192_{Ir}	15 at 2.0mm for vessel 3.0-4.0mm	Ongoing
Leon Instent restenosis, Native coronary arteries	GAMMA-1	Multicenter, Double blind Randomized, n=250	192_{Ir}	8-30 to the media according to IVUS	Significant advantage of brachytherapy. Higher risk of late thrombosis[20]
Kuntz De novo	BETA-CATH	Multicenter, Double blind Randomized, n=1100	90_{Sr-Y}	14-18 at 2mm	Significant advantage of beta radiation in PTCA and Stent arms when analyzed separately. Insignificant change in combined group.
Verin De novo		Multicenter, Open label n=1100	90_{Y}	9-18-32 at balloon surface	Brachytherapy not only prevents restenosis but induces luminal enlargement[21]
Raizner De novo	PREVENT	Multicenter, Double blind Randomized N=105	32_{P}	16-20-24 at 1mm	Significant reduction in restenosis in treated group. Higher incidence of myocardial infarction due to thrombosis
Popma Instent Restenosis	START	Multicenter, Double blind Randomized, n=396	90_{Sr-Y}	16-20 at 2mm	Significant advantage of brachytherapy without thrombotic event
Waxman Instent restenosis, Native coronary arteries	BETA WRIST	Single center, open label	90_{Y}		Significant reduction in restenosis in treated group
Serruys De novo, Multi-vessel	BRIE	Multicenter, open label n=100	90_{Sr-Y}	14-18 at 2mm	Ongoing
Fischell /Isostent	IRIS IA	IRIS IA Multicenter open label in 32 patients	32_{P}	low activity (0.5-0μCi) mean 0.69 μCi	Excellent feasibility, safety without thrombosis or subacute closure.
Mosses De novo Restenotic, Palmaz-Schatz	IRIS IB	Multicenter, open label n=100	32_{P}	activities 0.7-1.5□Ci (mean 1.14)	Excellent feasibility, safety without any subacute closure at 3 months. Angiographic restenosis > 35%
Hehrlein Restenotic, Palmaz-Schatz	Heidelberg	Single center, Open label n=15	32_{P}	activities 3.0□Ci	No major adverse clinical events at a mean follow-up of 4 months. Angiographic restenosis > 35%
Colombo / Isostent	Single center higher activity safety study	BX™ 15 mm coronary stent	32_{P}	activity 3.0 & 6.0 μCi	No major adverse clinical events. Restenosis rate high at the edges of the stent

With a follow-up extending for more than 3 years, the only significant events relate to the presence of 2 coronary pseudo-aneurysm[14]. Although the progression of these vessel abnormalities is unknown, it should be mentioned that dosimetry analysis revealed that significant higher doses were in fact delivered to the coronary arteries (19-55 Gy). The Geneva group reported a feasibility trial using an β isotope (^{90}Y) with a centering balloon, and a target dose of 18 Gy at the luminal surface in 15 patient's[15].. No adverse event occurred but the restenosis rate remained in the usual range. The reason for this negative outcome is conjectural, but it is the first study of endovascular irradiation carried out with a balloon centering device. The balloon centering system may be detrimental, particularly with beta radiation because it:may displace the vessel wall from the radioactive guide wire coil, creating a situation in which the vessel wall is dosed at less than 4 Gy; potentially compresses the vessel wall, making the tissues hypoxic and more resistant to the effect of ionizing radiation; may create additional injury to the vessel wall. Although increased homogeneity of the dose delivered to the vessel wall may be achieved with a centering device, there does not appear to be a pre-clinical or clinical study which justifies the need for an active centering system.

The BERT trial, a feasibility study performed jointly by Emory University-Rhode Island Hospitals, the Montreal Heart Institute and the Thorax center recruited 85 patients to evaluate a β source 90 Sr(Y), randomized between 3 doses 12, 14 and16 Gy at 2mm depth in denovo leasions[16]. A total of 78 patients received radiation and had their 6 months angiographic follow-up. Target Lesion Revascularization was needed in 11 patients. The dichotomous Restenosis Rate at the lesion site (defined as 20 mm centered by the lesion) was 16.7%, 13/78 patients. Also reported were 6 new lesions in the intervention area (defined as 30 mm centered by the lesion). The Late Loss Index for the 78 patients was less than 9%. Moreover, an IVUS sub-study performed in Montreal elucidate the mechanism of restenosis prevention: inhibition of hyperplasia and absence of any remodeling[17].

Finally, the most recent and last pilot trial reported with Beta radiation is the Proliferation Reduction with Vascular Energy Trial (PREVENT). This trial used the Phosphorous-32 on a 0.018 in wire with a 27mm source length. The doses were 0, 16, 20 and 24 Gy at I mm to prevent restenosis in lesions less than 15 mm treated with a balloon and / or a stent of (22 mm in length. Of the 43 patients (11 at 0 Gy) with complete follow-up, the Late Loss Index was at 4 % in the treated group versus 40 % in the 0 Gy group. Restenosis rate at the lesion site in the radiated group was 2/32 versus 2/11 lesions in the 0 Gy group. However, an "edge effect" was recognized with a restenosis in the adjacent segment of the lesion site of 5/32 in the treated group versus 1/11 in the 0 Gy group. There was also a report of death related to a stent occlusion at 2 months.

The first randomized trial was performed at the Scripps Clinic in 55 patients recruited for stent restenosis[18]. Using ^{192}Ir and a maximum dose of 8 Gy to the closest adventitia (IVUS guided), restenosis rate dropped to 17% in irradiated vessels as compared to 55% for controls. Similarly, IVUS demonstrated a significant reduction in neointima formation at 6 months after endovascular irradiation (18 ± 22 mm^3 vs 45 ± 39 mm^3). Furthermore, target lesion revascularization rates were 11.8 % for the active group and 44.8 % for the placebo group, a 74% reduction in this clinical endpoint. Two clinical complications were reported: one subacute thrombosis at 17 days in the active group and one cardiac death at 8 months within the placebo group. The late loss index in this study was 12% in the irradiated vessels and 60% in the controls.

Waksmann et at. reported at the 1998 American Heart Association (AHA) meeting 1998, the Washington Radiation In stent restenosis trial (WRIST) where hundred natives and 30 saphenous vein graft vessels were treated either with an active(Iridium192) or inactive (placebo) radiation source. The length of the source used was 19, 36 and or 52mm. The prescribed dose was 15Gy at 2mm for vessel under 4mm in diameter and 15Gy at 2.4mm for larger vessel. Restenosis Rate at 6 month was dramatically reduced, 15% in the active group compare to 48 % in the placebo group. The Late Loss Index went from 69% in the non active to 16% in the active treatment. All the clinical events were significantly reduced, TLR by 79%, TVR by 6% and any MACE at 6 months by 63%.

The IRIS IA study evaluated ^{32}P radioactive stents implanted in 32 patients with de novo lesions or restenosis[19]. With these low activity stents (0.51-1.0 μCi), excellent feasibility was demonstrated without thrombosis or stent occlusion. The angiographic restenosis rate at 6 months was 31%. Higher doses, up to 15 μCi, are investigated in Europe showing absence of neointimal proliferation inside the stent but proliferation and negative remodeling just outside the stent, the "Candy Wrapper" effect.

Several multicenter randomized trials are ongoing (cf. tables) and will clarify the potential of radiation therapy in the next 2 years for the prevention and/or the treatment of restenosis.

Conclusion

There is growing evidence that ionizing radiation is indeed effective in reducing neointima formation and probably in preventing negative vessel remodeling and hence, effective in reducing restenosis. Short-term experience with γ-rays seems to indicate a therapeutic window in human, which will need to be confirmed on a

long-term basis. Large ongoing trials using β and γ sources will bring new information during the next 2 years. Of paramount importance in this field are the dosimetry and radiation biology aspects, which will require to set-up multidisciplinary teams to further explore this fascinating new application of an old therapy.

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