Experimental therapeutic strategies in restenosis and critical limb ischemia

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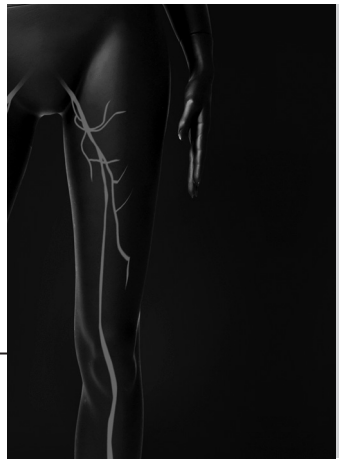

Chapter 02

Radiotherapy for peripheral vascular disease: an overview

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Abstract

The response of cells to ionising radiation has been extensively studied for the past 30 years. When radiation is absorbed in biological material, it can directly ionise a critical site (direct effect) or interact with other molecules to produce reactive free radicals, which can subsequently damage critical biological molecules (indirect effect). DNA is considered the critical target damaged by ionising radiation by both direct and indirect processes. Since radiotherapy had proven to be effective in the treatment of non-malignant proliferative processes, it was assumed that this adjunctive treatment would also inhibit vascular restenosis. The major difference between external and intravascular radiation is dose distribution. Intravascular delivery results in extremely high doses to the lumen with a fall-off in dose as a function of distance from the source; whereas, external beam would deliver a uniform dose over the entire volume of tissue treated. Unlike in the coronary circulation most of the peripheral vessels treated are greater than 3 mm in diameter; in fact many are 7 to 10 mm in diameter. Since beta radiation is related to lower penetration properties and more heterogeneous distribution of radiation in comparison to gamma radiation, it was therefore necessary to use a gamma radiation source because it would be difficult to irradiate the sub-intimal tissue with a beta source centered in a large vessel. Radiation can and does have the potential to destroy blood vessels. The challenge in vascular brachytherapy was to treat blood vessels to a point where restenosis is inhibited; yet the vessel is not irreparably damaged.

Introduction

Restenosis remains the major problem after endovascular interventions for obstructive disease. After an intervention there are three components that influence the mechanism of restenosis. First, elastic recoil immediately after (over)stretching an artery.
This is an immediate effect and over time there is only minimal further progression of this elastic recoil. Second, restenosis caused by intimal hyperplasia. Most likely, this process starts after a few days and may continue for months to years. The third mechanism is elucidated as constrictive fibrosis. The entire artery may become contracted, resulting in a smaller lumen.[1-3]
Vascular injury causes a cascade of events leading to platelet aggregation and therefore thrombus formation, inflammation, and activation of monocyte-derived macrophages and smooth muscle cells. The smooth muscle cells are stimulated to rapid division by Transforming Growth Factor-(TGF-β) and/or Platelet Derived Growth Factor (PDGF), activated in response to damage to the endothelium. The cause of intimal hyperplasia appears to be the rapid proliferation of smooth muscle cells after migration from the media to the intimal layer. Besides that, a lesion of the vessel wall stimulates adventitial myofibroblasts proliferation and thereby α smooth muscle actin, leading to a fibrotic response in the adventitia.
Over the last 20 years the focus of restenosis treatment has been through application of pharmacologically active agents, mechanical devices and prosthetic technologies. Unfortunately most of these methods have proven to be of limited success in the battle against restenosis.
Since the discovery of radium by Madame Curie in 1898, ionizing radiation has been well known as an antiproliferative agent. Since radiotherapy had prove to be effective in the treatment of non-malignant proliferative processes such as the fibroblastic activity of keloid scar formation and ocular pterygia, it was assumed that this adjunctive treatment would also inhibit vascular restenosis. This was the beginning of a new field in medicine called vascular brachytherapy.
In 1994 it was Liermann *et al*. who performed and published the first cases of vascular brachytherapy in patients who had undergone a PTA of the femoropopliteal artery.[6] After these first clinical applications a lot of experimental work was performed by Wiedermann, Waksman and Mazur.[7-9]
Radiation can and does have the potential to destroy blood vessels (e.g. radiation for Hodgkin's disease and radiation for arteriovenous malformation). The challenge is to treat blood vessels to a point where restenosis is inhibited; yet the vessel should not be irreparably damaged.

Radiation biology

When radiation is absorbed in biological material, it can directly ionize a critical site (direct effect) or interact with other molecules to produce reactive free radicals, which can subsequently damage critical biological molecules (indirect effect). DNA is considered the critical target damaged by ionizing radiation (by both direct and indirect processes) by formation of exchange-type aberrations.

There is a dose-response linear-quadratic relation between the fraction of cells surviving and the dose. At low doses, the linear component dominates, but at higher doses, the term that is quadratic in dose starts to dominate.[10]

One of the most important consequences of exposure of biological tissue to ionizing radiation is the loss of the cell's ability to reproduce, which ultimately results in the death of the cell. Cell death should be distinguished from the intuitive concept we have of death: that is, complete and irreversible loss of all functions. While it is true that super-high dose of radiation (in the region of several hundred Gray) will certainly cause such an effect, lower radiation doses will not give such an effect. In fact, the vast majority of such irradiated cells appears morphologically normal and continues to perform complex biological functions including protein and DNA synthesis. However, in terms of continued health of that biological tissue, a proportion of these cells will lose their ability to sustain reproduction and will die at the next mitosis.[11]

Cells proliferate and multiply, therefore, individual cells traverse through a distinct cell cycle containing: mitosis, G1, S and G2 phase. Since the 60's it is already known that the cell radiosensitivity varies as a function of cell cycle position.[12] Cells in G2 and mitosis are the most radiosensitive, while cells in the late S phase are the most resistant to a given dose of radiation.

Taking the *in vitro* cell survival data of smooth muscles cell in to account it appears that a dose of 12 to 20 Gray is efficacious in preventing restenosis. From experimental systems it is documented that the biological effect of a given dose rate is decreases when the dose is delivered at a low dose over a longer period of time.[13]

A number of radionuclides have been under investigation for vascular brachytherapy. Some of the most commonly used are shown in Table I.

Table I. *Radionuclides under investigation for vascular brachytherapy.*

Radionuclide	Emission	Half-life
^{32}P	β	14 day
^{90}Y	β	2.7 day
$^{90}SR/^{90}Y$	β	29 year/2.7 day
^{103}Pd	X	17 day
^{188}RE	β	17 hr
^{188}W	β	60 day
^{102}Ir	γ	74 day

External beam radiation *versus* endovascular radiation

Ionizing radiation, to prevent restenosis after an intervention, can be administered in 2 fashions: by external beam irradiation or endovascular brachytherapy (therapy from a short distance). The main advantage of external beam radiotherapy is the homogeneity of dose distribution at the target field, with no overdose to specific layers. Another advantage is that this technique is noninvasive and therefore can be delayed for hours or days, at a time when more cells are proliferating. It also can be more efficiently fractionated in several doses. The major drawback of external beam radiation is the possible long-term effect on the irradiated vessels and the adjacent structures. In theory, these drawbacks could be eliminated with the use of stereotactic radiotherapy. There has been considerable controversy regarding the use of external beam radiation treatment to prevent restenosis. External beam irradiation is mainly used when a superficial location is involved such as the anastomotic sites of an AV dialysis shunt.[14]

The major difference between external and endovascular radiation is dose distribution. Endovascular delivery results in extremely high doses to the lumen with a fall-off in dose as a function of distance from the source (Table II); whereas, external beam would deliver a uniform dose over the entire volume of tissue treated. Therefore, endovascular irradiation is more suitable for blood vessels at a deeper location.

Endovascular irradiation can be delivered by catheter-bases systems immediately after an endovascular intervention (or by radioactive stents). Usually endovascular irradiation is delivered by an afterloader system. "Unloaded" tubes are positioned at the target site to be irradiated. Subsequently they are loaded with the radioactive source (hence the term "afterloader"). In the early days this aferloading was performed manually, but in the currently used "remote afterloaders" the radioactive source is stored in a shielded container and inserted into the tubes via a remote controlled afterloading device.[15] High-activity β or γ seeds, pellets, capsules and wires can be uses for this purpose. To provide a homogenous intramural radiation dose delivery, a special centering balloon was developed to assure optimal centering. Some spiral designs even permit continuous flow during the period of irradiation.

Table II. *Dose distribution for ^{192}Ir.*

Depth (mm)	Dose (cGray)
3	1200
4	877
6	551
8	396
10	303

Beta *versus* gamma radiation

Radioactivity is the process in which atomic nuclei spontaneously change their configuration and energy content. This event normally brings a change in the basic

element itself that is known as radioactive disintegration. This process is associated with emission of particulate or electromagnetic radiation. The particulate radiation is either γ emission or β emission. β particles are lightweight β particles and possess positive or negative charge. They can only travel through tissue over a limited distance. Gamma emission takes the form of electromagnetic radiation. The electromagnetic γ rays arise in the atomic nuclei and may have a very complicated spectrum consisting of many energy values.

In the cases of catheter-bases endovascular brachytherapy both β and γ sources are being used (Table I). β radiation is related to lower penetration properties and more heterogeneous distribution of radiation in comparison to γ radiation. There is an ongoing discussion about the ideal isotope for endovascular brachytherapy. Radiation protection issues and the possibility to use a β isotope in a regular angiosuite make this isotope an attractive choice. In coronary arteries the efficacy of β radiation is proven although dose-finding studies are still ongoing.

Unlike in the coronary circulation most of the peripheral vessels treated are greater than 3 mm in diameter; in fact many are 7 to 10 mm in diameter. It is therefore necessary to use a γ radiation source because it would be difficult to irradiate the subintimal tissue with a β source centered in a large vessel. The main reason for this is the less rapid fall-off dose of the γ with the distance from the source.[16] The dose distribution for ^{192}Ir is shown in Table II. The risk to the nearby nerves can be considered minimal.[17]

Although it would be possible to bring a high dose rate afterloader in the OR or angiosuite, room modifications necessary to meet radiation safety requirements make this impractical. Therefore treatment delivered by β radiation should take place in the radiation oncology department.

Clinical trials

After the experimental and animal brachytherapy studies, many investigators were encouraged to initiate clinical studies in humans. Although Liermann and Schopohl were the first to perform such a study, using radiation in the peripheral vascular system, most of the development in this field and, therefore most of the research, derived from studies in coronary arteries. Following numerous studies that examined feasibility and the short-term safety, several large randomised trials generated the evidence of effectiveness in reduction of intimal hyperplasia. Initially in the cardiac setting, later in the peripheral vascular field.

Coronary arteries

Both β and γ emitters were used in the clinical trials for intracoronary brachytherapy. Although ^{192}Ir is the only γ emitter in use, a large variety of β were tested, such as ^{32}P, ^{90}Y, ^{90}SR/^{90}Y, ^{188}Re and ^{188}W. Radiation doses ranging from 8 to 30 gray were used, as well as a variety of delivery systems. The clinical studies using β emitters were initially carried

out to prevent in-stent restenosis. Later trials were designed to study the effectiveness in preventing restenosis in *de novo* lesions. The search for the ideal isotope and/or the most favorable has been ongoing. Based on the result of three randomised clinical trials using γ radiation, the investigators of these studies considered this therapy standard therapy for patients presenting with in-stent restenosis in the coronary arteries.[18-20] The most important randomised clinical trials using either β or γ emitters are summarized in Table III. At the time there were no randomised studies on radioactive stents.

Table III. *Randomised clinical trials using catheter-based intracoronary brachytherapy for native coronary and in-stent restenosis.*

Study	No.	ISR lesion	Source	Dose (Gy)	Follow-up (mth)	Restenosis (%) EBT	Restenosis (%) Placebo	P-value
Teirstein[18,21] (97/00)	55	ISR	^{192}Ir	26	36	33	64	<0.05
Waksman[19] (2000)	130	ISR	^{192}Ir	15	6	19	58	0.001
Raizner[20] (2000)	105	N	^{32}P	16,20,24	6	8	39	0.01
Leon[22] (2001)	252	ISR	^{192}Ir	30	9	22	51	0.01
Popma[23] (2001)	476	ISR	^{90}SR/Y	18 or 23	8	27	45	0.002
Waksman[24] (2002)	332	ISR	^{32}P	20	9	26	52	0.0001

N= de novo; ISR= in-stent restenosis; EBT= endovascular brachytherapy

Peripheral arteries

In the peripheral vasculature only γ radiation by a ^{192}Ir radiation source is feasible. Some randomised controlled studies showed very significant results in the superficial femoral artery after 6-12 months follow-up.

All randomised clinical trials using γ emitters in the peripheral arteries are summarized in Table IV.

Table IV. *Randomised clinical trials using irradiation therapy after PTA in the femoropopliteal artery.*

Study	No.	lesion	Source	Dose (Gy)	Follow-up (mth)	Restenosis (%) Radiation	Restenosis (%) Placebo	P-value
Minar[25] (2000)	113	N/R	^{192}Ir	12	6	28	54	<0.05
Zehnder[26] (2003)	100	R	^{192}Ir	12	12	23	42	0.03
Pokrajac[27] (2005)	134	N/R	^{192}Ir	18	12	42	67	<0.05
Tongeren[28] (2005)	60	N	^{192}Ir	14	12	35	44	0.51
Wolfram[29] (2005)	88	N+S	^{192}Ir	14	12	33	35	0.89
Diehm[30] (2005)	83	N/R	^{192}Ir	14	36	36	53	0.16
Wolfram[31] (2006)	102	N/R	^{192}Ir	12	60	73	73	0.99
Fritz[32] (2004)	95	N/R	EBI	21	12	46	33	0.29
Zabakis[33] (2005)	60	N+S	EBI	24	12	47	80	0.02
Therasse[34] (2005)	99	N	EBI	7,10,14*	12	65,48,25*	50	<0.001*
Zampakis[35] (2007)	60	N+S	EBI	24	36	55	71	0.04

N=de novo; R=recurrent; S=stent *only significant after 14 gy

Conclusions

With vascular brachytherapy an exciting era was entered for the interventionist in the battle against restenosis. Many questions were still to be answered, but the short term results were more than promising. At the time, many cardiology centers embraced this new technique as a standard, adjunctive treatment for some of their interventions and initiated a close co-operation with the radiotherapists. Peripheral vascular brachytherapy, and therefore using γ radiation, made this technique more cumbersome. Especially for these cases requirements and health care milieu regulations were very demanding.

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