Reviews

Brachytherapy for Treatment of Restenosis after Percutaneous Coronary Intervention

Proven therapy or premature application of technology with unknown long-term effects?

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As the number of percutaneous coronary interventions (PCI) increases every year, the need for an effective treatment of restenosis becomes more obvious. The evolution of PCI, especially the widespread use of stents, has allowed more and more patients with coronary artery disease to be treated effectively and safely since the majority of the acute complications of PCI can be treated in the cardiac catheterization laboratory without emergency CABG. However, restenosis remains a difficult problem to treat[1,2].

Over the last several years intracoronary radiation of treated by PCI stenoses by gamma or beta radiation (brachytherapy) has been proposed as the most effective treatment for restenosis. The suggested beneficial effect of brachytherapy is the inhibition of smooth muscle proliferation and possibly the favorable arterial wall remodeling. Based on limited experimental data, the first clinical trial of gamma radiation for restenotic lesions was designed and completed with impressive results regarding reduction of new restenosis[3]. A series of other clinical trials with both gamma and beta radiation followed, all of them with favorable results regarding six month restenosis recurrence (Table 1)[4-6].

However, after the initial enthusiasm a more detailed analysis of the clinical data, as well as longer follow up of the patients revealed several problems and raised concerns regarding the long-term effectiveness and safety of this treatment. Detailed experimental studies also increased these concerns further in view of the increased clinical application of brachytherapy. In this review we will attempt to place brachytherapy on a more realistic outlook, based both on experimental and clinical data without the enthusiasm that every treatment of restenosis generates.

Technical problems and safety

Although brachytherapy is technically simple, it poses several difficulties for widespread application because of safety concerns for both patient and cath lab personnel and the time required for its use. Handling radioactive material requires several safety precautions, especially for gamma radiation. Additional to routine shelding of the cardiac catheterization laboratories might be required. Radiation sources (Ir or Sr) have limited half-life, so renewal is necessary. Handling is required to be done by a radiation physicist, while advancing the catheters in place requires in many places a radiation oncologist. Treatment time required is 3-10 minutes for beta and 20 minutes for gamma radiation, in addition to time required to advance and remove the catheters.

Table 1. Randomized clinical trials of brachytherapy for restenosis.

	Radiation	Patients	Angiographic restenosis (%)	
			Brachytherapy	Placebo
SCRIPPS	gamma	55	21	46
WRIST	gamma	130	23	60
GAMMA-I	gamma	252	32	55
START	beta	476	29	45

Apart from safety all the above measures increase procedural time and cost. Therefore, such a treatment with several logistic problems and cost must be particularly effective and safe to be clinically useful.

Subacute and late stent thrombosis

From the initial phase I and II brachytherapy trials, as well as, from the subsequent randomized trials it appeared that subacute and even late thrombosis could occur in higher percentage than expected[7]. The term subacute thrombosis is used for events occurring from 30 days to 6 months, while late thrombosis to events after 6 months. In GAMMA-1 trial in the brachytherapy group thrombosis occurred in 13.5% of patients compared to 5.8% in placebo. The mechanism of thrombosis is not entirely clear in humans. In experimental studies it was found delayed endothelial regeneration leaving uncovered the thrombogenic stent surface most likely responsible for thrombosis.[8] There is evidence that the inhibition of endothelial regeneration can be permanent. Based on such data, it appears that our understanding of stent endothelialization after brachytherapy is limited and that the time at risk for thrombosis has not accurately been defined. It should be emphasized that brachytherapy not only inhibits the growth of smooth muscle cells but the growth and regeneration of the cells of all layers of the arterial wall, with all the expected consequences. Currently long term antiplatelet treatment with aspirin and clopidogrel or ticlopidine is necessary.

Arterial wall weakness and aneurysm formation

A well-documented consequence of brachytherapy is the aneurismal dilatation of the arterial wall. This is considered the result of arterial wall weakness and remodeling. It has been observed after high radiation dosage and at least for the first few months after the procedure the arterial size appears increasing. The long-term progress of such areas is unknown, with limited data suggesting stabilization after 2-5 years[9]. A similar phenomenon is considered the appearance by intravascular ultrasound of "black holes" adjasent to stents. In such cases full stent-wall apposition was documented immediately after stent placement, but in follow up arterial wall weakness led to late loss of apposition. The exact prevalence of this phenomenon remains unclear, as well as its significance for stent thrombosis.

Edge effect

From the first studies of brachytherapy with angiographic follow-up it became clear that restenosis was more frequent at the edges of the stent. Several names have been used to describe this phenomenon, like candy wrapper effect and it appears that it is due to the mitotic stimulation of low dose radiation, which occurs at the edges of the radiating segment of the catheter[10,11]. This phenomenon decreases significantly the benefit of brachytherapy and requires another treatment. It has been suggested that apart from the reduced radiation dose at the edges of the stent, endothelial trauma is also necessary. For preventing it longer segments of the arterial wall should be radiated, but even this has not solved the problem entirely.

Long-term inflammatory reaction and negative remodeling

There is experimental data showing that although endothelial regeneration following brachytherapy is reduced for 6-12 months, in several cases an inflammatory reaction follows later with neoendothelial

hyperplasia. In essence, restenosis was not inhibited but delayed in time. It has also been observed that in 1-3 years negative remodeling could occur. In clinical studies with follow-up up to 5 years such events have not been observed, although lumen loss has occurred beyond 6 months, a phenomenon opposite to what usually happens with PCI without brachytherapy[12]. It should be noted that the total number of patients followed after brachytherapy is small and that the time required for humans to show similar reactions to experimental animals is different and probably longer. Therefore, similar problems in humans cannot be excluded in time. Theoretically we cannot even exclude long term neoplasias like soft tissue sarcomas, something rather unlikely.

Conclusions

All the above leave several questions regarding the proper use of this technology in clinical practice. Is brachytherapy a proven treatment for restenosis after PCI with potential widespread use, or it was an idea whose time has passed? The correct answer seams to lye between these two extreme positions. It is obvious that brachytherapy is the only proven therapy for restenosis today, although without the capability to eliminate this problem entirely. It has been suggested that the difference between the groups of brachytherapy and placebo was influenced by the routine angiographic follow-up required in most studies. Without angiography the difference in clinical restenosis could be less between the two groups.[13]

Brachytherapy should be considered as a new extremely interesting technique, which however is still in its childhood. Its widespread use is not supported by the existing data today. A much larger number of patients are required with longer follow-up for phenomena, which might not be obvious by now. Until then the medical community should view brachytherapy with skepticism and its application should be limited to specialized centers only. This was the recommendation of FDA also, when they approved the clinical use of this technology in the USA.

References

1. Fischman DL, Leon MB, Baim DS,et al: A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994; 331: 496-501.
2. Serruys PW, de Jaegere P, Kiemeneij F, et al: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994; 331: 489-495.
3. Teirstein PS, Massullo V, Jani S, et al: Catheter-based radiotherapy to inhibit restenosis after coronary stenting. N Engl J Med 1997; 336: 1697-703.
4. 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: 2165-2171.
5. Raizner AE, Oesterle SN, Waksman R, et al: Inhibition of restenosis with beta-emitting radiotherapy: report of the Proliferation Reduction with Vascular Energy Trial (PREVENT). Circulation 2000; 102: 951-958.
6. 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.
7. Waksman R, Bhargava B, Mintz GS, et al: Late total occlusion after intracoronary brachytherapy for patients with in-stent restenosis. J Am Coll Cardiol 2000; 36: 65-68.
8. Salame M, Verheye S, Mulkey SP et al: The effect of endovascular irradiation on platelet recruitment at sites of balloon angioplasty in pig coronary arteries. Circulation 2000; 101: 1087-1090.
9. Condado JA, Waksman R, Gurdiel 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.
10. Schwartz RS, Koval TM, Edwards WD, Camrud AR, Bailey KR, Browne K, et al: Effect of external beam irradiation on neointimal hyperplasia after experimental coronary artery injury. J Am Coll Cardiol 1992; 19: 1106-1113.
11. Hehrlein C, Kaiser S, Riessen R, Metz J, Fritz P, Kubler W: External beam radiation after stent implantation increases neointimal hyperplasia by augmenting smooth muscle cell proliferation and extracellular matrix accumulation. J Am Coll Cardiol 1999; 34: 561-566.
12. Terstein 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.
13. Sheppard R, Eisenberg MI: Intracoronary radiotherapy for restenosis. N Engl J Med 2001; 344: 295-296.