Intracoronary brachytherapy for restenosis: an efficient technique in the struggle for survival?

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In the last few years intracoronary radiation has emerged as an effective antirestenotic therapy in percutaneous interventional cardiology.

Radiation, by damaging the DNA of the nucleus, inhibits cell proliferation non-selectively, mostly during mitosis and the G2 phase of the cell cycle[1]. Intravascular radiation, at sufficient doses to the arterial wall, can inhibit proliferation of smooth muscle cells and fibroblasts in the media and adventitia, in response to an arterial injury and additionally, by preventing adventitial fibrosis, it avoids negative arterial remodelling[2,3]. This was shown to be highly effective in experimental animal models, both with gamma and beta sources and doses of 10–30 Gy targeted at the tunica media[4,5].

In the last 5 years, several randomized clinical trials and registries have been published[6–13], using different brachytherapy (meaning, a short distance between the source and target) systems[3]. The gamma sources (mainly with iridium-192) were the first to be used. They are more penetrating, allowing a more homogeneous distribution between superficial and deep layers of the arterial wall, but are potentially more harmful to neighbouring tissues. The handling of the sources is more complicated for all personnel, requires a 25-mm lead screen and evacuation of the laboratory during the dwell time for treatment, of around 30 min. The solid beta sources (yttrium-90, strontium/yttrium-90, phosphorous-32) penetrate in tissue only a few millimetres, allow a more localized treatment in several sites, and the handling of the source and radioprotection measures are much simpler. The need for centring of the beta source within the arterial lumen is still controversial and one solution is the use of liquid beta sources (rhenium-188 and 186) injected into the angioplasty balloon catheter. Radioactive stents (phosphorous-32) have also been used and although conceptually very attractive the clinical results have been disappointing mainly
due to restenosis of the stent edges, even with the use of ‘cold’ ends[14].

From all studies it can be concluded that intracoronal radiation is safe, efficient in reducing restenosis in the target segment, but have two significant intrinsic limitations: late thrombosis and edge restenosis[15,16].

The delayed re-endothelization after arterial trauma constitutes a potential problem, as the treated segment will become, temporarily, more vulnerable to thrombus formation. The potential late thrombotic complications are, however, no longer a problem, as it seems they have been solved with prolonged antiplatelet treatment (recommendation of use of aspirin and clopidogrel for at least 6 months) and avoiding stent implantation after irradiation.

The main limitation is, still, the so-called ‘edge effect’, mainly seen with the radioactive stents, but also present with both gamma and beta radiation. It results from balloon injury and/or low-dose radiation or dose fall-off (called geographic miss by the radiation oncologists) at the edges of the treated segment, all possible mechanisms stimulating neointimal proliferation. One way of probably reducing it, is to use long source trains, leaving large (4-10 mm) margins on either side of the target segment[16].

Apart from these known limitations, there are still several unknowns with radiation therapy, such as optimal dosing (a privileged field for IVUS guided radiation dosing which has yet to be fully explored), centring delivery, long-term clinical risks and adverse effects on vessels (IVUS observations of unhealed dissections, late malapposition and ‘black hole’ phenomenon[17], etc. Patient selection is, perhaps, the most interesting point for discussion: should brachytherapy be used as an adjunct to initial balloon/stent angioplasty, or should it be kept for some forms of in-stent restenosis?

The paper by Serruys et al. in the current issue of the journal[18], report further on the results of a multicentre European registry on the use of the Beta-Cath® system known as the BRIE study[19]. This has a 30 mm source (strontium/ytrrium-90) for de novo and restenotic lesions. Their results mirror present knowledge of brachytherapy outside the setting of in-stent restenosis. The study shows effective inhibition of treated segment restenosis (for lesions with an average length of 11 mm, binary restenosis, excluding total occlusions, was 4.9%) and for patients treated with balloon alone, there was positive remodelling at follow-up. The edge effect was responsible for 29% of restenosis of the irradiated segment and the geographical miss was responsible for 75% of the edge failures or 40% of the restenosis observed in irradiated segments. Radiation was performed after balloon angioplasty with a provisional stent, but in 74% of cases there were post-radiation interventions, with 96% of all implanted stents in the study, which was responsible for 53% of the incidence of geographical miss. Late vessel occlusions occurred in 5-3% (eight vessels, seven with stents and one balloon), but this reduced significantly when antiplatelet drugs were given for 8 weeks–6 months. The authors suggest the use a balloon-to-source ratio of 1:2 (the longer the better) and that radiation should be planned as the last intervention. The study confirms that geographic miss is the main pitfall of brachytherapy.

The use of brachytherapy for in-stent restenosis, particularly of the diffuse pattern with the highest recurrence rates, has attracted most clinical research in the U.S.A. Based on the results of several randomized clinical trials, with gamma and beta emitters, brachytherapy was approved by the FDA in November 2000 for in-stent restenosis; it has since then become the first line therapy for diffuse stenosis. Both in-stent rerestenosis and target lesion revascularization have shown significant reductions with radiation vs placebo. Interestingly, this edge was effect less of a problem, perhaps due to the initial high ‘malignancy’ of diffuse in-stent restenosis.

Radiation therapy is not easy to implement and some catheter laboratories and hospitals will never have it. Its use requires a team where radiation oncologists and physicists are important legal partners, perhaps limiting more widespread use of the technique. The choice of radiation source has logistic implications, as gamma would require modifications in the normal setting, special shielding and a treatment time avoiding the presence of medical personnel. Fortunately, comparisons between gamma and beta radiation did not show superiority of one over the other and, therefore, beta seems more attractive, simpler and safer.

For the lucky ones who can have brachytherapy, the future looks bright with new radiation systems (i.e. the source of P32 encapsulated in the distal 27 mm of a nitinol wire)[20] and the association of synergistic techniques (i.e. rotational atherectomy followed by radiation with rhenium-188-mercaptoacetyltriglycine-filled balloon)[21], etc., being developed.

The first clinical results of sirolimus eluting stents[22] brought a new wave of hope to percutaneous coronary interventions. Sirolimus inhibits the proliferation of vascular smooth-muscle cells through G1/S transition of the cell cycle and, so far, no restenosis or significant side effects have occurred. It seems somewhat unfair that after more than 10 years of experimental and clinical work and after being
considered as the first real antirestenotic therapy, brachytherapy should find itself, following the appearance of sirolimus stents, in a struggle for survival.

If a programme of intracoronary radiation is already available in your hospital, you will have to find niches for its use, but if you have not yet implemented it, it may be time to wait and see. Until the promise of niches for its use, but if you have not yet implemented in your hospital, you will have to find ready available in your hospital, you will have to find ready available in your hospital, you will have to find appearance of sirolimus stents, in a struggle for survival. The search for control of restenosis seems to be finally at an end, as we now have two equally effective antiproliferative therapeutic forms of controlling restenosis after coronary interventions.

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References