Current Perspective

Long-Term Efficacy of Intracoronary Irradiation in Inhibiting In-Stent Restenosis

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Background—Intracoronary irradiation is a promising modality for inhibition of in-stent restenosis. Results of randomized clinical trials at 6 months after gamma ray irradiation are highly encouraging. The first results at 3 years after irradiation, while still showing benefit, have shown significant late loss. The probable mechanism of the radiation is to inactivate (prevent from dividing) most cells that otherwise could proliferate to produce neointimal formation. We measured the proportion of cells that survive with their clonogenic potential intact after the doses and dose rates used in the randomized trials, and we then modeled the subsequent repopulation of the surviving cells that might cause late restenosis.

Methods and Results—Human aortic smooth muscle cells were irradiated with gamma rays, including the doses and dose rates used in current trials, and clonogenic surviving fractions were measured. The subsequent repopulation of the surviving cells was modeled with the assumption that the repopulation kinetics were similar to those in unirradiated cells. The radiation is expected to delay the time to restenosis by factors of ≈ 6 to 8, depending on the dose, shifting the delay from a median of 6 months (for no irradiation) to median values from 36 months (for a nominal 13 Gy) to 43 months (for a nominal 15 Gy).

Conclusions—These results and predictions are quantitatively consistent with clinical results and suggest that clonogenic inactivation (prevention of cellular division) is the dominant mechanism of radiation action in the delay of restenosis. Intracoronary radiotherapy is a very promising modality for significantly delaying, although probably not preventing, in-stent restenosis. (*Circulation.* 2001;103:1330-1332.)

Key Words: radiotherapy ■ stents ■ coronary disease ■ restenosis

There is considerable interest in intracoronary gamma irradiation to inhibit in-stent restenosis, and randomized trials have been initiated. Several of these trials have reported significant clinical and angiographic advantages over control subjects with 6-month follow-up times.[1,2] More recently, the SCRIPPS study (Scripps Coronary Radiation to Inhibit Proliferation Post Stenting) has reported results with 2 and 3 years of follow-up.[3,4]

Longer follow-up is important because there is some evidence from the 2-year follow-up of the Washington WRIST trial (Washington Radiation for In-Stent restenosis Trial),[2] from long-term results in irradiated peripheral arteries,[5] and from theoretical considerations[6] that late (>6 month) restenosis after intracoronary irradiation may be significant. The theoretical background is that the radiation doses being used would be expected to inactivate (ie, prevent from dividing) most but not all of those target cells that would otherwise cause early restenosis; however, those cells that survive the radiation exposure may eventually divide and repopulate sufficiently to cause restenosis.

In fact, the recently reported 3-year follow-up results,[4] although still showing a favorable outcome, indicate a significantly reduced advantage relative to control subjects compared with the 6-month results: the 3-year results show only statistically borderline superiority over control subjects for restenosis ($P=0.07$; all values calculated exactly with Fisher's exact test rather than the asymptotic values reported by Teirstein et al[4]) or for target vessel revascularization ($P=0.06$), although they remain significantly advantageous for target lesion revascularization ($P=0.01$).

We report here the first direct measurements of the proportion of cells that survive with their clonogenic potential intact after intracoronary irradiation, and we model the subsequent target cell repopulation. The results suggest that for those individuals in whom restenosis would have occurred in the "classic" 2- to 8-month period after dilation, gamma radiation, as delivered in current published randomized trials,[1–4] will increase these times to restenosis by factors of 6 to 8, depending on the dose; thus, intracoronary radiation produces a major delay in the onset of, but probably does not prevent, in-stent restenosis.

Methods

We measured the proportion of cells that survive with their clonogenic potential intact after the radiation doses (and dose rates) delivered in the current intracoronary radiation trials. Normal aortic

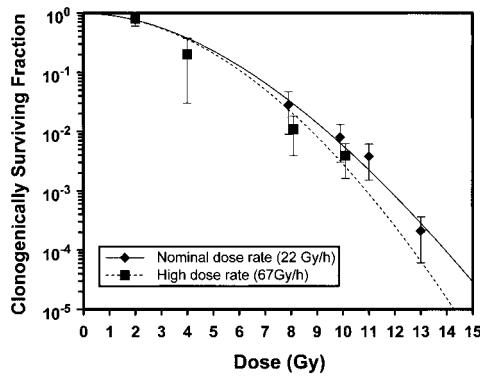*Circulation* is available at http://www.circulationaha.org

Figure 1. Measured surviving clonogenic fraction of cells as a function of dose and dose rate for exponentially growing normal human aortic SMCs. ♦ indicates measurements at a nominal dose rate typically used in the clinic (22 Gy/h at 2 mm from luminal center)[1,2]; ■, measurements at high dose rate (67 Gy/h). Curves refer to a single, global fit of all data to Equation 1 at both the nominal dose rate (solid curve) and high dose rate (dashed curve).
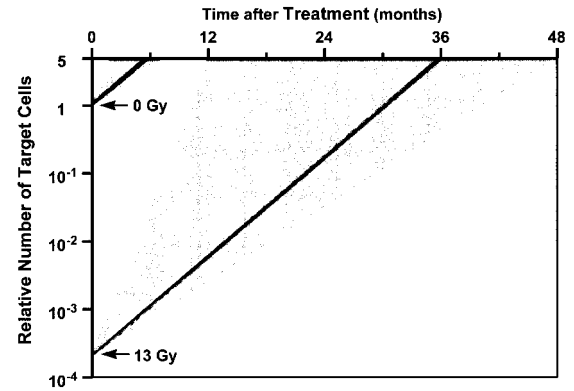

Figure 2. Predicted repopulation kinetics as function of time after treatment for individuals who fail (with target lesion revascularization) after stent implantation. Kinetics are shown for patients receiving zero-dose or a nominal radiation dose of 13 Gy (at 2 mm from luminal center) in 35 minutes. As discussed in text, a relative number of target cells of 5 (compared with that at the time of stent implantation) is considered to represent a treatment failure. Solid lines indicate median values; shaded area covers 90% of those patients who will experience failure.

smooth muscle cells (SMCs) derived from a 54-year-old man were used. Although SMCs are a likely target cell responsible for in-stent restenosis, other possible target cells are likely to have comparable radiosensitivity.[6]

Following the guidelines of the American Association of Physicists in Medicine task group,[7] the normalized dose at 2 mm from the center of an assumed 1.5-mm-radius lumen was taken as the nominal dose, nominally in the middle of the media. The estimated mean dose at this point in the SCRIPPS study[1,3,4] was 13 Gy,[7] delivered over 20 to 45 minutes.[1]

Exponentially growing human aortic SMCs were exposed in vitro to graded doses, up to 13 Gy, of gamma rays, delivered both at a high dose rate (67 Gy/h) and at dose rates comparable to that in the SCRIPPS trial (13 Gy at 2 mm in 35 minutes).[1,7] Following standard protocols,[8] the clonogenically surviving fraction relative to the zero-dose control cells was measured.

To model the kinetics of the subsequent repopulation of the surviving clonogenic cells, we first assumed that a factor-of-5 increase in the number of target cells relative to those present in an unirradiated population will produce restenosis. This value is based on simple geometric considerations regarding the luminal area of the arterial region at risk,[6] but because our results are scaled from clinical data (see below), the final predicted results are not very sensitive to the actual factor assumed, within reasonable limits. We also assumed that the rate of repopulation of the cells surviving the radiation exposure is the same as that which, in the unirradiated population, leads to restenosis. This is likely to be a conservative assumption in that the radiation exposure could be a trigger of accelerated repopulation, but this effect is expected to be small at the doses of relevance here.[9] We have estimated the rate of repopulation in unirradiated target cells using clinical results for target lesion revascularization as a function of time after stent implantation (without radiation), as reported by Fishman et al[10]; in that study, 90% of all target lesion revascularizations occurred between ≈1.9 and 7.6 months (median, 5.8 months).

Results

The measured radiation-induced clonogenic surviving fractions are shown in Figure 1, together with a single, global fit of all the data to the linear-quadratic model:

(1) $$S=\exp(-\alpha D-G\beta D^2),$$

where

(2) $$G=2(T/\tau)^2[(T/\tau)-1+\exp(-T/\tau)]$$

Here, S is the surviving clonogenic fraction at dose D; T is the exposure time; and α, β, and τ are free parameters. G is a dose-rate-reduction factor, which is 1 for an instantaneous dose, 0 for an extremely prolonged dose, and an intermediate value for other situations. The parameter values obtained were $\alpha=0.021$ Gy^{-1}, $\beta=0.061$ Gy^{-2}, and $\tau=44$ minutes.

The measured clonogenic surviving fraction at 13 Gy delivered in 35 minutes (simulating the SCRIPPS study,[1,3,4] as discussed above) was $2.1\pm1.5\times10^{-4}$. Although this value corresponds to a dose at one given depth (2-mm depth in a 1.5-mm-radius lumen), a simple calculation confirms that this is representative of the weighted average survival from 1.5- to 2.5-mm depth.

Figure 2 shows the clinically assessed repopulation kinetics in those unirradiated (0 Gy) patients who failed (with target lesion revascularization) after stent implantation[10]; also shown are the corresponding predicted repopulation kinetics after a 13-Gy dose, if the proportion of cells that survived the radiation with their clonogenic potential intact was 2.1×10^{-4}, as measured. The radiation is predicted to shift the median time to restenosis from 5.8 months in the unirradiated population to ≈36 months in the irradiated population. Likewise, it is predicted that 90% of all restenoses occurring after the radiation exposure will occur between 12 and 48 months, in contrast to the 90th percentile of ≈2 to 8 months in the unirradiated population.

Discussion

At doses relevant to intracoronary irradiation, the most relevant mechanistic end point is the inability of a cell to clonogenically divide. The mechanisms for this process are well established, being dominated by the production of exchange-type chromosomal aberrations, such as dicentrics and centric rings, that drastically reduce the ability of a cell to divide.[11]

On the basis of measurements of the proportion of target cells that survive with their clonogenic potential intact at the

doses and dose rates currently used, it is predicted that radiation will significantly delay, but probably not prevent, the onset of restenosis. Quantitatively, the gain in the delay to restenosis in the SCRIPPS study[1,3,4] is predicted to be ≈6-fold, increasing the median time to restenosis from ≈6 months (for the unirradiated group) to ≈36 months, with 90% of the restenoses in the irradiated group occurring between ≈12 and 48 months. These predictions are consistent with the clinical data[4] in which a marked loss of efficacy at 36 months was reported relative to the results at 6 months after irradiation.[1]

A higher dose will produce still larger delays. For example, in the Washington WRIST study,[2] a dose of 15 Gy was delivered in ≈30 minutes at 2 mm from the center of the lumen. On the basis of the fit (equation 1) to the data in Figure 1, an initial clonogenic depopulation of ≈3×10^{-5} would be expected and, on the basis the same kinetics as above, a median time to restenosis of ≈43 months (compared with 36 months for a 13-Gy nominal dose) would be predicted. This represents a significant gain for a modest dose escalation.

It is important to note that normal human cells have a limited capacity to divide; a figure of 50 ± 10 cellular divisions (the "Hayflick limit") in embryonic cells, decreasing to just a few in old age, has been suggested.[12] This finite cellular division capability may explain why almost three quarters of unirradiated dilated patients do not restenose[10]; more divisions could be needed to produce a restenosis than are possible in these adults. In irradiated vessels, even more cellular divisions would be required to produce restenosis, so it is possible that radiation could actually reduce the ultimate frequency of restenoses[6] as well as delay their occurrence; future clinical data may support or refute this suggestion, although the clinical data to date[4] do not currently lend it strong support.

In conclusion, we have measured the proportion of cells that survive with their clonogenic potential intact after the doses and dose rates used in clinical trials of intracoronary brachytherapy. These data, together with an experimentally based model of the subsequent target cell repopulation, predict that radiation to a nominal gamma ray dose of D Gy (at 2 mm from the center of the lumen) will delay the time to restenosis by a factor of about D/2, shifting the delay from a median value of about 5.8 months (for no irradiation) to median values of 36 months (for 13 Gy) to 43 months (for 15 Gy).

These quantitative conclusions should allow for improved evidence-based decisions regarding the optimum dose and expected long-term outcome of intravascular radiotherapy. The conclusions are qualitatively and quantitatively consistent with current clinical results, lending support to the suggestion that radiation-induced inhibition of cellular division is the dominant mechanism of action and confirming that high-dose radiation is a most promising modality for significantly delaying, although probably not preventing, in-stent restenosis.

Acknowledgments

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