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Radiosensitivity Testing of Normal Tissues: a Way to Optimise Radiotherapy?

P. Lambin and P. Lawton

IN THIS issue, Floyd and Cassoni (pp. 615–620) assessed the reliability of a lymphocyte micronucleus assay to determine the radiosensitivity of individual patients. Levels of radiation-induced micronuclei were measured following exposures of up to 4 Gy X-rays. The variation between individuals was greater than between repeat experiments on the same individual and, in accordance with the literature, they found that cord blood lymphocytes were generally more radiosensitive than normal lymphocytes. The authors conclude that the lymphocyte micronucleus assay could have some predictive capacity for the determination of individual radiosensitivity. Unfortunately, it is difficult to be certain as to whether or not the conclusions of Floyd and Cassoni are generally valid. Lymphocytes are a heterogeneous cell population, especially with regard to the proportion of lymphocytes subtypes. Furthermore, they die after irradiation both by reproductive death and by apoptosis, in contrast to the majority of cell types which die mainly by a reproductive death. Despite these limitations, this is an important study. We urgently need a reliable assay for predicting the radiosensitivity of normal tissues before radiotherapy is commenced. In order to achieve this, it is essential to understand the relationship between the *in vitro* radiosensitivity of different cell types and the clinical response to radiotherapy.

A subpopulation of radiosensitive patients

There is evidence to suggest that both tumours and normal tissues show interindividual differences in intrinsic radiosensitivity. In 1975, Taylor and colleagues noted a correlation between the cellular radiosensitivity of skin fibroblasts and severe reactions to radiotherapy in an individual with the genetic disorder ataxia teleangiectasia (AT) [1]. There have now been a number of published retrospective studies of individuals showing severe reactions to radiotherapy where cultured fibroblasts have shown excessive *in vitro* radiosensitivity [2–4].

AT is a rare genetic disorder but it has been estimated that about 1% of the population are carriers for the AT gene. These

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individuals may be more sensitive to radiation and are more likely to develop cancer than the normal population [5]. It has been suggested that as many as 18% of all patients with breast cancer may carry the AT gene [6], so that there may be selection for this gene in the irradiated population.

Optimisation of radiation therapy

The possible benefit of a change in treatment strategy must always consider simultaneously the effects on tumour response and on normal tissue damage, i.e. the therapeutic index. Tolerance doses of radiation are currently set on the basis of injury occurring in a determined minority of the patient population. The 5% or so of patients who suffer major radiation injuries essentially limit the dose that is delivered to all the irradiated patients. It has been calculated that removing the 5,10 or 15% of the most radiosensitive patients from the treated group would allow higher radiation doses to be given to the remainder without increasing overall complication rates [7]. This study suggests that tumour control rates could be considerably improved even if genetically determined variations in radiosensitivity were expressed to the same extent in both normal tissue and tumour cells. The radiosensitive patients will not necessarily be denied radiation therapy. Rather, they would probably receive therapy but with some reduction in dose per fraction and total dose that corresponds to the increase in radiosensitivity found for their normal cells. It might then be possible to treat the remaining patients to a higher dose level.

Which assay should be used?

Several small studies have suggested that *in vitro* fibroblast radiosensitivity, measured in a clonogenic assay, predicts for late normal tissue effects seen in patients [2, 4]. This technique, however, takes 6–8 weeks to obtain a result. But compared to fibroblasts, lymphocyte assays offer the advantages that the method is rapid (results can be obtained within 1 week) and samples can be easily obtained from peripheral blood rather than from a skin biopsy. This makes the lymphocyte an attractive cell type for prospective radiosensitivity testing studies. But the relevance of lymphocyte radiosensitivity for the clinic is still controversial. Lymphocyte cultures have been used to confirm the radiosensitivity of AT compared to normal individuals [8]. DNA damage and repair in freshly drawn blood samples have been measured using nuclear-lysate sedimentation [9]. With this technique, the lymphocytes of a patient with T cell lymphoma, who was unusually radiosensitive during radiotherapy, showed no restoration of sedimentation behaviour when irradiated *in vitro* [10]. In a comparison of lymphocyte repair in healthy donors versus cervix carcinoma patients presenting with bowel complications, Deeley and Moore [11] demonstrated poor repair in 7 and 44%, respectively.

On the other hand, some authors [4, 12, 13] did not find a correlation between radiosensitivity of lymphocytes and fibroblasts. Furthermore Geara and colleagues [4] did not find a significant correlation between lymphocyte radiosensitivity and either acute or late effects clinically evaluated in patients.

In conclusion, there is evidence that patients differ significantly in their radiosensitivity and, more specifically, that the fraction of sensitive patients could be higher in the cancer population. The removal of this radiosensitive subpopulation might allow clinicians to treat the rest more aggressively without any increase in complications and with an improvement in local tumour control. The data so far suggest that the *in vitro* radiosensitivity of fibroblasts does correlate with the late effect of radiation in clinical practice. An assay using lymphocytes would have several practical advantages, but the clinical relevance of this model must still be evaluated prospectively in a population of irradiated patients.

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