Commentary

Radiation Induced Lymphocyte Apoptosis: An Effective Way of "Tailoring" Radiotherapy to the Right Patients Only?

CrossMark

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Late radiation-induced side effects are a major concern for both clinicians and patients, owing to their frequent irreversibility and possibly permanent detrimental effect on quality of life. Despite technological refinements simply unimaginable less than 10–15 years ago, a significant fraction of patients still experience severe long-term sequelae after radiotherapy. It is surprising to observe how in some cohorts of subjects treated on the same anatomical site, with identical radiation doses and techniques and with comparable doses unavoidably delivered to healthy tissues surrounding the tumor, only a minority of subjects occasionally develop dramatic late sequelae, while all the others pass through irradiation with no, or only minimal, negative consequences. Such a phenomenon is explainable only by hypothesizing the existence of individual radiosensitivity.

In their elegant paper in this issue of *EBioMedicine*, Azria et al. report on the first prospective, multi-Institute trial investigating the role of Radiation Induced Lymphocyte Apoptosis (RILA) as a predictor of breast fibrosis after adjuvant radiotherapy following breast conservative surgery (Azria et al., 2015).

RILA, defined as the percentage of peripheral blood lymphocyte (PBL) death induced by a certain radiation dose minus the spontaneous cell death (Ordonez et al., 2014), is a versatile, rapid and reproducible assay of radiosensitivity on PBL (Crompton and Ozsahin, 1997; Ozsahin et al., 2005). In general, radiobiological normal tissue assays are technically more convenient and feasible than tumor tissue assays (Azria et al., 2012). Lymphocytes, in particular, appear to be the ideal candidates for such analyses, owing to both their accessibility and

high concentrations in peripheral blood (Azria et al., 2012). As previously reported, though only in a retrospective manner or in prospective single-Institute studies (Ordonez et al., 2014; Ozsahin et al., 2005; Azria et al., 2008; Bordon et al., 2010; Foro et al., 2014) an inverse relationship between the percentage of apoptosis in irradiated lymphocytes and late toxicity emerged also in this report (Azria et al., 2015). The mechanism of this inverse association is not completely clear, being possibly related to the delay of cells in recognizing the radiation-induced cell damage and initiating apoptosis, with a consequently increased risk of toxicity and, theoretically, of cancer radioresistance and reduced tumor control.

In particular, a decreased incidence of Grade ≥ 2 breast fibrosis was observed by Azria et al. for increasing values of RILA, while no Grade 3 breast fibrosis was observed in patients with RILA > 12%, with a negative predictive value of 91% for RILA ≥ 20%. The positive predictive value was, on the contrary, much lower (22% for RILA ≤ 12%) (Azria et al., 2015). This finding, far from weakening or reducing the translational significance of this trial, simply suggests that, as appropriately highlighted by the Authors (Azria et al., 2015), a biological assay is not, in itself, sufficient to predict the risk of late effects. In the French multicentric study, treatment-related and behavioural factors (namely, adjuvant hormonal therapy and tobacco smoking) also emerged as strong predictors of complication-relapse-free-survival (CRFS) (Azria et al., 2015).

On the contrary, and as previously described (Ozsahin et al., 2005), no correlation emerged between RILA and acute toxicity, leading the Authors to postulate that mechanisms other than DNA repair are represented by the RILA assay (Azria et al., 2015).

No predictive value emerged for RILA with respect to oncological outcome. This is not surprising, given the overall favorable prognosis of the analyzed cohort, in which clinical relapses and deaths occurred in only 2.6% and 1.1%, respectively, of the cases. As emphasized in the paper, breast cancer is of course not the most appropriate cancer in which to evaluate the possible prognostic significance of RILA, which has been demonstrated, on the contrary, in more aggressive neoplasms such as cervical (Ordonez et al., 2014) and prostate carcinoma (Foro et al., 2014), though not confirmed in a prospective Swiss study on 399 patients with miscellaneous cancers (Ozsahin et al., 2005). Undoubtedly, the possible association between the radiosensitivity of normal tissues and clinical outcome deserves further thorough investigation (Ordonez et al., 2014).

The Authors are to be commended for their efforts to thoroughly investigate the possible existence of an intrinsic individual radiosensitivity which may ultimately predict an enhanced and aberrant individual

susceptibility to radiation injury. More in general, the moment appears to be fast approaching when both RILA and/or well defined networks of Single Nucleotide Polymorphisms (SNPs), other promising though less reproducible and of more complex interpretation markers of both radiosensistivity and radioresistance (Azria et al., 2008; Reuther et al., 2015), will allow the selection of patients with a reasonably low risk of late radiation-induced sequelae, given their promising negative predictive value. This achievement would be of enormous clinical importance, especially for those tumors (e.g. prostate cancer) for which radiotherapy represents a valid alternative to surgery. Once similarly excellent clinical outcomes achievable with both treatment modalities are ascertained, the preferences of prostate cancer patients are in fact strongly impacted by the fear of side-effects (Avila et al., 2015).

The availability of quick, easy and reproducible tools able to improve the prediction of the excessive or reduced risk of a given subject's developing well-defined late sequelae would be of inestimable value for both patients and clinicians, especially for tumors such as lung, prostate, head and neck cancers and sarcomas, for which dose-escalation has a well-documented role.

Disclosure

The author declared no conflicts of interest.

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