One Size Fits All: Does the Dogma Stand in Radiation Oncology?
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External beam radiotherapy (EBRT) is the most treatment used in solid tumors as nearly 50% of cancer patients receive curative EBRT in the world. Its success depends mainly on the total dose homogeneously delivered within the target volume. Nevertheless, EBRT inevitably exposes surrounding normal tissues and may cause late and sometimes irreversible toxicities depending on different cells or tissues (stroma, vascular, parenchymal, immune cells). Interactions between cells or tissues (stroma, vascular, parenchymal, immune cells) define those toxicities. A fixed-effects meta-analysis identified genetic markers of toxicity. A recent review by Herskind et al. (2016), pathway analyses incorporating different ‘omics’ approaches may be more efficient in identifying critical pathways than those based on single ‘omics’ data sets. Integrating these pathways with functional assays may be powerful in identifying multiple subgroups of EBRT patients characterized by different mechanisms. In that way, monocentric cohorts suggested that radiation-induced CD8 T-lymphocyte apoptosis (RILA) as a functional test can predict late toxicity after curative intent EBRT. We recently assessed the role of RILA as a predictor of breast fibrosis (bf+) after adjuvant breast EBRT in a prospective multicenter trial (Azria et al., 2015). A total of 502 breast-cancer patients (pts) treated by conservative surgery and adjuvant EBRT were recruited at ten centers. RILA was assessed before EBRT by flow cytometry. Impact of RILA on bf+ (primary endpoint) or relapse was assessed using a competing risk model. With a median follow-up of 38.6 months, grade ≥ 2 bf+ was observed in 64 pts (14%). A decreased incidence of grade ≥ 2 bf+ was observed for increasing values of RILA (p = 0.012). No grade 3 bf+ was observed for patients with RILA ≥ 12%. Negative predictive value for grade ≥ 2 bf+ was equal to 91% for RILA ≥ 20% where the overall prevalence of grade ≥ 2 bf+ was estimated at 14%. A significant decrease in the risk of grade ≥ 2 bf+ was found if patients had no adjuvant hormonotherapy (sHR = 0.31, p = 0.007) and presented a RILA ≥ 12% (sHR = 0.45, p = 0.002). Different hypotheses to understand the mechanisms of inverse correlation between low radiation response of lymphocytes and the increase risk of developing late reaction after EBRT are currently under investigations: (i) Production of cytokines and inflammatory immune cells attraction to the irradiated tissue.
(Azria et al., 2008); (ii) Protein and ROS production modification, enhanced genomic instability, terminal differentiation of fibroblasts and increased risk of fibrogenesis (Lacombe et al., 2013); (iii) genetic defect in the DNA damage response, DNA repair reduction, increased genomic instability and increased premature terminal differentiation of fibroblasts (Herskind et al., 2016).

Clinical implementations with interventional protocols are starting using this assay permitting distinction between patients without any over-risk of toxicity (considered as resistant to late effects) and patients clearly at risk of developing more late effects defined as very sensitive (Barnett et al., 2015). In terms of altered management, hyperfractionation can reduce toxicity with no risk of loss of local control or to allow for dose escalation in very sensitive patients. For more resistant patients, an increase in dose should be possible and hypofractionation regimen should be largely proposed leading to a medicoeconomic improvement of our treatments. This might be in favor of adding novel targeted or existing systemic therapies (Barnett et al., 2015).

In conclusion, there is no doubt that personalized radiotherapy driven by companion tests of radiotoxicity but also of tumor radioresponse will be the standard of care in the near future as it is already the case for targeted therapies in medical oncology. One size will no longer fit all!

Disclosure

The authors declare that they have no competing interest regarding this manuscript.

References


