To exploit the 5 'R' of radiobiology and unleash the 3 'E' of immunoediting: 'RE'-inventing the radiotherapy-immunotherapy combination

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How radiotherapy counters immune evasion

In conventional radiotherapy (RT), the relative biologic effectiveness of radiation is influenced by radiobiological determinants, the so-called '5Rs': Repair, Repopulation, Redistribution, Reoxygenation, and Radiosensitivity.[1] A linear-quadratic model prevails to describe the radiation response of the tumor, in which the α/β ratio is used to characterize the sensitivity of a particular tissue type to fractionation. Fractionation serves to decrease acute, and especially late, toxicity to surrounding normal tissue exposed to RT. Commonly, curative RT is delivered in daily doses of 1.8–2.2 Gy for 5–8 weeks, whereas hypofractionation is defined as a delivery of greater than 2.2 Gy per fraction. With sophisticated advances in RT technologies, delivering higher doses of RT per fraction [i.e. increased biologically effective dose (BED)] in a shorter timeframe appears a safe option. Indeed, increased BED could be achieved with larger fraction sizes relative to conventionally fractionated RT. While early radiobiological studies had found that the major mechanisms of action of radiation were related to DNA damage and subsequent cell death of dividing cells, novel insights on radiation effects have uncovered the immunomodulatory properties of ionizing radiation.[2]

From immunosurveillance to immunoediting

The concept of 'Cancer immunoediting' has been refined, along with the understanding of the dual host-protective and tumor sculpting actions of immunity. This process is comprised of three phases, termed the '3 Es of Cancer immunoediting': Elimination, Equilibrium, and Escape. Through these phases, tumor immunogenicity is edited, and immunosuppressive mechanisms that enable disease progression are acquired. Therefore, the clinical presence of a tumor suggests a failure in elimination, and progression to equilibrium or escape. Various forms of immunotherapies (e.g. vaccines, delivering effector cells, immune checkpoint blocking antibodies) are currently designed to shift the balance from equilibrium and escape to elimination.[3] Yet, only a small proportion of patients may actually benefit from these treatment options as malignancies either respond poorly or are completely resistant. The precise timing of immunotherapy administration in combination with traditional cytotoxic approaches, as well as treatment duration, are still elusive and will require further optimization depending on the mechanisms of immune therapy.

How to synergize radiation and immunotherapy?

Optimal approaches to achieve tumor elimination will involve therapeutic combinations to promote immune activation and T cell priming, suppress immunosuppressive signals in the tumor microenvironment and sustain the presence of T cells within the tumor tissue. It is then tempting to tailor immunotherapies with RT to synergize innate and adaptive immunity against cancer cells as well as to bypass immune tolerance and exhaustion.[4] While a plethora of ongoing clinical trials is presently assessing the efficacy and the safety of these combinations, the rationale of these associations is based mainly on few preclinical data and relies on individual properties of each modality. Nonetheless, from an arithmetic progression point of view, one can wonder whether the clinical potential of the radiotherapy–immunotherapy

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combination should be defined as '5R + 3E', suggesting an additive effect of the combo, or whether it should be further specified as '5R × 3E, arguing that radio-immunotherapy acts in a synergistic manner. In this context, there are many logistical aspects that should be considered in order to better exploit the 5R and to unleash the 3E. At the time of confluence of radiotherapy with immunotherapy, are we at an inflection point for the use of conventional RT?

(1) At the level of fractionation and total dose: is daily irradiation obsolete and should it be substituted by hypofractionated schemes for longer periods or lower doses? In this combination setting, is there any rationale to maintain standard widths of margins?
(2) At the level of radiation delivery: should we expect more clinical benefit from particle-beam therapy using protons or carbon ions? There is some evidence showing that charged particles may be more immunogenic than photons because these species may distinctly mobilize cell death pathways and damage response pathway induction.
(3) At the level of site irradiation: is it time to abandon single site irradiation to move towards gross irradiation when multiple disease sites are present? Is the irradiation of draining lymph nodes optimal for triggering the immunogenic effects of radiation?
(4) At the level of immune activation: should sequential combinations of immunomodulators with RT be planned? Should we trigger immunogenic responses through partial tumor irradiation?[5]

Many questions await answers such that we must 'RE'-visit or 'RE'-invent our basic principles of RT to guide innovative therapies capable of improving local tumor response to RT and of enhancing the abscopal effect through an *in situ* vaccination, as RT could act as a systemic treatment against distant metastasis.

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