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Editorial

Turning Radiotherapy into an Effective Systemic Anti-cancer Treatment in Combination with Immunotherapy

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Radiotherapy is a major part of cancer treatment, with over 50% of all cancer patients receiving this treatment. The focus in delivering radiotherapy, whether for palliation or as part of potentially curative therapy, has been on inducing direct tumour cell death, resulting in the goal of local tumour control. However, in addition to the direct cytoreductive effect of radiotherapy, emerging evidence suggests that radiotherapy can generate anti-tumour immunity [1,2]. Radiotherapy-induced tumour cell death leads to increased ecto-calreticulin and tumour antigen expression as well as the release of several damage-associated molecular patterns (DAMPs). These 'danger signals' include high mobility group box 1 and ATP and can lead to the recruitment and activation of antigen presenting cells and priming of tumour antigen-specific T cell responses [3,4]. Despite these immunostimulatory properties of radiotherapy, systemic anti-tumour immune responses leading to clinical anti-tumour responses outside of the irradiated tumour field (called the 'abscopal effect') are rare in routine clinical practice [5]. The lack of a clinically meaningful abscopal effect is thought to be secondary to the immunosuppressive nature of the tumour microenvironment including myeloid-derived suppressive suppressor cells, Foxp3 T regulatory cells (Tregs) or blocking inhibitory molecules such as PD1 or CTLA4 receptors and inhibitory cytokines including transforming growth factor-beta and interleukin-13 ([6] and references therein). Therefore, therapeutic strategies designed to overcome these inhibitory immunosuppressive networks may provide an opportunity to enhance anti-tumour immunity by promoting the generation of T cell priming in combination with radiotherapy (Figure 1).

Real progress leading to the development of effective anti-cancer immunotherapy has been achieved in recent years with the application of the emerging new biological insights concerning the importance and nature of immune checkpoints that are able to reverse the downregulation of anti-tumour immunity. These immunomodulatory agents can be divided into either agonists or immune stimulating receptors (co-stimulatory receptors, e.g. anti-CD40, OX40, anti-CD137) or antagonists of immune suppressor molecules (co-inhibitory molecules, e.g. anti-CTLA4, anti-PD1, anti-PDL1 [6]). It is this latter class of therapeutics, termed 'checkpoint inhibitors', that has gained much attention recently in oncology, with monoclonal antibodies targeting molecules such as CTLA4 and PD1, which play a pivotal role in the negative regulation of T cell activity. Durable long-term responses were initially observed in some patients with advanced metastatic melanoma, initially with the anti-CTLA4 monoclonal antibody, ipilimumab [7].

More recently, anti-PD1 or anti-PDL1 monoclonal antibody have delivered durable remissions in patients with melanoma and renal cancer, non-small cell lung, bladder and head and neck cancers, providing genuine optimism that immunotherapeutic approaches can improve outcomes in a wide range of cancers [8,9]. The PD1/PDL1 axis is involved in the maintenance of peripheral tolerance and modulation of acute inflammatory responses through the inhibition of T cell function, such as loss of T cell receptor signal transduction, or through apoptosis of activated T cells. PD1 upon interaction with its ligands, PDL1 and PDL2, initiates an inhibitory signalling network that switches off activated T cells and results in T cell exhaustion or anergy leading to poor effector function, even in the presence of antigens or apoptosis (see Figure 1) [10]. Although barely detectable in most normal tissues, expression of PDL1 has been described in multiple malignancies ([11] and references therein).

The manageable tolerability of anti-PD1 monoclonal antibody pathway blockers and their unique mechanism of

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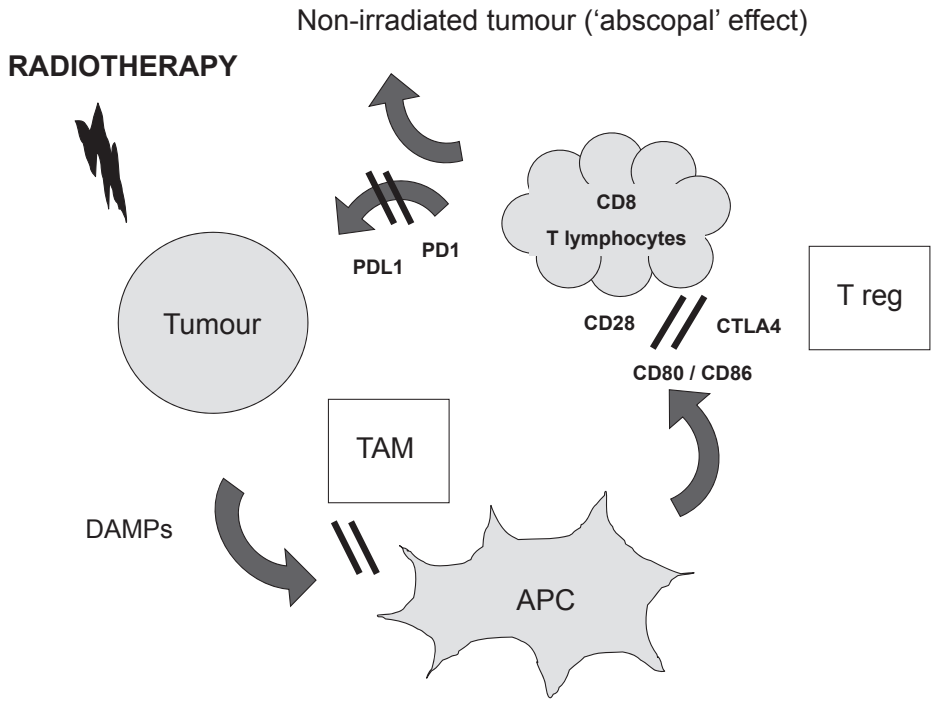

Fig 1. Overview of the anti-cancer immune response after radiotherapy and how combination with immunomodulatory agents may enhance the generation of anti-cancer immunity. After treatment with radiotherapy, tumour cells undergo immunogenic cell death characterised by the release of damage-associated molecular pattern (DAMP), which promotes antigen presentation by antigen presenting cells (APC) such as dendritic cells. This in turns leads to priming of a tumour-specific CD8+ T cell response (CD80 and CD86 from APC acting through CD28 on T cell). Immunomodulatory agents can be used to enhance activation of APC (e.g. TLR7 agonists), promote T cell activation by blocking inhibitory receptors (e.g. CTLA4) or counteract adaptive resistance mechanisms within the tumour microenvironment which limit T cell function (e.g. PD1/PDL1) and tumour associated macrophages (TAMS). Tumour cells may express PDL1, the ligand for the inhibitory PD1 receptor found on T lymphocytes. Thus, radiotherapy and immunomodulatory agents, for example anti-PD1 can co-operate to enhance the generation of durable T cell responses and anti-cancer immunity.

action are encouraging, but combination therapy approaches will be required to improve response rates further for most patients. Radiotherapy is attractive for such combinations, given the local anti-tumour efficacy and lack of systemic immunosuppression commonly seen with systemic agents. The biological premise here is that radiotherapy will cause local tumour cell kill leading to tumour antigen release that will promote a specific tumour adaptive immune response. This radiotherapy-induced immune response will be augmented by immunomodulatory agents, leading to systemic anti-tumour immunity. Numerous preclinical studies have confirmed the potential for clinical translation of radiotherapy and immunomodulatory agents (reviewed in [6,12]). Considerable interest in the potential generation of systemic anti-immunity of radiotherapy in combination with immunomodulatory agents was stimulated by a case report in 2012. A patient with metastatic melanoma had developed progressive disease despite ipilumumab (anti-CTL4 monoclonal antibody inhibition). However, after palliative radiotherapy a systemic response with regression of lung metastases was seen with further ipilumumab [13]. Subsequently there have been several further case reports and small phase I/II studies ([14] and reviewed in [15]) also reporting such abscopal effects. Interestingly, these data suggest that local responses to radiotherapy may be predictive of abscopal responses. Overall, these results suggest that radiotherapy after immunoregulatory agents may lead to abscopal responses in some patients with advanced melanoma correlating with prolonged overall survival, providing optimism that radiotherapy can enhance the systemic anti-immune response. Further larger and randomised trials are needed to validate these promising initial results about the role of radiotherapy in enhancing systemic immune responses. There are many ongoing studies including the UK National Cancer Research Institute phase III study of anti-PD1 (Pembroluzimab) versus localised radiotherapy and anti-PD1 in metastatic malignant melanoma, which is shortly to open nationally investigating this phenomenon in a randomised manner.

Currently a significant challenge in further developing immunoregulatory agents in the clinic is to better understand the mechanisms of resistance in the majority, who currently fail to achieve clinically meaningful responses. For radiotherapy and immunoregulatory agent combinations, a key question is how and when radiotherapy increases the number of durable anti-tumour immune responses. From the radiation oncology perspective it is of paramount importance to explore mechanisms to better understand how combinations with immunodulatory agents might improve tumour control and outcome for radiotherapy for both radical and palliative treatments. Recent mechanistic