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Mini-review

Immune modulation in advanced radiotherapies: Targeting out-of-field effects

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ABSTRACT

By virtue of being a localized treatment modality, radiotherapy is unable to deliver a tumoricidal radiation dose to tissues outside of the irradiated field. Nevertheless, ionizing radiation may result in radiation damage mediated by a bystander like effect away from the irradiated field, but this response is likely to be modest when radiotherapy is the sole treatment modality. Over the last decade there has been a re-emergence of immune modulating therapies as anti-cancer treatment modalities. Clinical trials on vaccines have on the whole been largely disappointing, but greater response rates have been observed from the immune checkpoint modulators. A clinical benefit of using such agents has been shown in disease sites such as melanoma and non-small cell lung cancer. There is growing pre-clinical data and a number of case reports which suggest the presence of abscopal effects when radiotherapy is co-administered with immune checkpoint inhibitors, suggesting that this combination may lead to an enhanced tumour response outside of the primary treatment field. In this review, the mechanisms of such an enhanced out-of-field tumour response, the potential clinical utilities, the optimal radiotherapy delivery and considerations for clinical follow-up following treatment are discussed.

Introduction

In the last decade technological advances have permitted more accurate delivery of radiotherapy to target sites within the body, which reduces damage to the surrounding normal tissue and allows radiotherapy dose escalation to maximize curability [1]. High dose, high precision and hence highly localized radiotherapy to tumour sites outside of the brain is known as stereotactic ablative body radiotherapy (SABR) [2]. SABR has been used to treat primary lung cancer with comparable control rates to surgery [3,4]. SABR is also used in the treatment of oligometastatic disease, where a patient has only a small number of metastatic sites detected by conventional imaging [5]. As the name suggests, SABR delivers high dose, hypofractionated treatment and hence an ablative dose. For example, in the treatment of early stage lung cancer, regimens of 54–60 Gy in 3 fractions are delivered in just over a week which is in stark contrast to a standard dose of 60–66 Gy delivered in 30–33 fractions over 6 weeks [6]. In consideration of the tolerance of the adjacent normal tissues SABR treatments are relatively free from significant toxicity or side-effects [6]. However, in the high dose region, the ablative dose leads to intense radiation damage and hence a significant tissue response with an associated immune response (e.g. for a patient receiving 54 Gy in 3 fractions with a maximum dose of up to 130% within the target volume, will in effect receive a biologically equivalent dose (BED) of up to 227 Gy, assuming an α/β ratio of 10) [7]. This immune response can be observed clinically in lung SABR treatments as pneumonitis, which can develop into fibrosis in the surrounding normal lung [8]. Although this immune response to radiation is clearly undesirable, it may be possible to harness this effect and use it to target cancer cells not irradiated within the primary tumour.

In conjunction with the recent advances in radiotherapy delivery, over the last decade there has also been a greater understanding of the immune response to malignancy which has led to the development of a number of immune modulating agents [9,10]. Agents such as the immune checkpoint modulators have been shown to lead to regression of a number of solid malignancies and in some cases, to a prolonged complete response to treatment [11].

Radiation induced bystander effect has been used to describe the phenomena whereby non-irradiated cells exhibit the features of cells that have been directly irradiated [12]. These bystander induced effects can include chromosome alterations, altered gene expression, apoptosis, increased radiation resistance or sensitivity and neoplastic transformation [13]. The exact underlying mechanism of the bystander effect has been difficult to elucidate in patients but may be due in part to an immune mediated response. The abscopal effect may be a possible clinical manifestation of this in which an enhanced tumour response is observed in disease locations which

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are outside of the primary treatment field [14,15]. More recently, there have been a growing number of case reports demonstrating the presence of abscopal effects when radiotherapy is co-administered with immune checkpoint inhibitors [16–18], implying that the ablative nature of radiotherapy treatment leads to an immune response which is augmented by these immune modulating agents [19]. The underlying cellular mechanisms driving the immune response to radiotherapy may be due in part to the irradiated tissue release of danger associated molecular pattern molecules or 'DAMPs' such as double-stranded DNA, RNA, chromatin, or high-mobility group protein1 (HMGB-1) [20]. These DAMPs are then recognized by toll-like receptors (TLR) which in turn activate integral components of the immune system such as macrophages [21].

One area of potential clinical use of the combination of SABR and immune modulating agents is in the setting of oligometastatic disease [22]. The term oligometastatic, initially suggested by Hellman and Weichselbaum, describes the presence of a limited number of metastatic sites of disease, usually less than 6 in number [23]. In de novo or induced oligometastases eradication of the oligometastases may lead to long term survival [24]. In this setting the potential of enhanced in-field radiotherapy delivery may lead to an increased chance of long term control and even if a patient's disease is not truly oligometastatic, and if there are clinically undetectable metastases elsewhere. In this setting it is suggested that immune mediated out of field responses may prevent progression of non-irradiated undetectable metastasis and may lead to an increased chance of a complete response. This review considers possible mechanisms of such an enhanced out of field tumour response, the potential clinical utilities, optimal radiotherapy delivery, the timing of immune modulation and any considerations for clinical follow-up after treatment.

The immune response to malignancy

The immune system can detect and respond to the presence of malignant cells [10,25]. This immune response to cancer can be activated by the presence of antibodies to antigens on malignant cells, from tumour specific T-cells and tumour infiltrating lymphocytes [26–28]. It has been shown that in some cancers, the presence of tumour infiltrating immune cells correlates with clinical outcome [29]. Despite the response mounted by the immune system, tumours may develop multiple mechanisms to evade the host immune system surveillance [30]. These include inhibition of tumour antigen presentation, secretion of immunosuppressive cytokines, recruitment of immunosuppressive cell types and inhibition of attack by immune cells [25,31]. The evasion of immune destruction has been added as an emerging parameter in the repertoire of cancer hallmarks [32].

Immunotherapeutic approaches in the treatment of cancer

Modulation of the immune system and intervention in the cancer evading mechanisms may be a potential therapeutic strategy. Immunotherapeutic strategies can be considered as either active or passive. Passive approaches involve the use of exogenous effectors of an immune response such as humoral anti-tumour antibodies (e.g. trastuzumab targets and binds to the extra-cellular domain of the HER-2/neu receptor inhibiting downstream signalling) or by a cellular adoptive approach such as allogeneic transplantation [33]. Active approaches include non-specific immune modulation, therapeutic vaccines, modulation of T-cell function and oncolytic viruses. Examples of these are shown in Table 1 [34–52].

Non-specific immune stimulation has been in routine clinical use for over a decade with the use of interferon-α and interleukin-2 in the treatment of diseases such as melanoma and renal cell carcinoma. These agents act by modulating the immune system rather than by a direct cytotoxic effect [34]. Both agents act primarily by modulating the immune system rather than by a direct cytotoxic effect, and are non-specific, and producing significant side-effects, such as fatigue and fever, with modest clinical benefit [35,37,53]. In contrast, vaccine therapy is highly specific and directed against whole cells, or towards specific tumour antigens [54]. Despite early positive signals of response, larger studies of vaccine therapy both in the palliative or adjuvant setting have been on the whole disappointing and it is likely that vaccine therapy monotherapy will not be efficacious as a single strategy in anti-cancer treatment [55–58]. Oncolytic viruses, such as Talimogene laherparepvec, selectively infect and kill the malignant cell of interest [52], and have a dual mode of action as they also trigger an endogenous reprogramming of the immune response against malignant cells. The induction of the latter process causes antigen presentation of infected malignant cell components which may then become immune targets.

Of emerging clinical interest are agents which modulate T-cell function. It has been shown that tumours can evade and then escape the immune system by producing immunosuppressive cytokines of the type-1 interferon signalling pathway (type-1 IFN) either from the tumour cells directly or from cells within the tumour microenvironment [58,59]. These immunosuppressive cytokines lead to T-cell inactivation and hence a loss of immune response. A number of immune checkpoint inhibitors such as the anti-CTL antigen-4 (CTLA-4) or anti-programmed death-1 (PD-1) antibodies, which inhibit these cytokines by a number of mechanisms, have been used in clinical trials. Examples of such agents are listed in Table 1 [45,48]. CTLA-4 is crucial in maintaining tolerance to self-antigens, hence preventing auto-immune disease and is a master regulator of T-cell activation [60]. In malignancy and in the milieu of the tumour microenvironment CTLA-4 acts to reduce or inactivate the T-cell response. Normal immune response T-cell activation requires the binding of the T-cell receptor to a presented antigen and co-stimulation of the T-cell by the binding of CD28 to CD80 and CD86 on the surface of the antigen presenting cell. CTLA-4 competitively competes with the CD28/CD80/CD86 complex on antigen presenting cells, and in the tumour micro-environment where CD80 and CD86 are depleted, transmitting an inhibitory signal to T-cells [60]. CTLA-4 is also expressed on CD4+ regulatory T cells which are also known as (Tregs). On Tregs CTLA-4 induces the production of the highly suppressive cytokine transforming growth factor beta which also acts to down-regulate T-cell function [61]. Thus CTLA-4 has a key role in reducing T-cell mediated immunity. Mono-clonal antibodies

Table 1
Examples of active immunotherapeutic approaches.

Non-specific immune stimulation	• Cytokines (e.g. interleukin-2, interferon-α) [34–36] • Killer-cell immunoglobulin-like receptor antagonists [37] • Indoleamine 2,3-dioxygenase (IDO) pathway inhibitors [38]
Therapeutic vaccines	• Sipuleucel-T (prostate carcinoma) [39] • Anti-MAGE-A3 vaccine (non-small cell lung cancer and others) [40] • Racotumomab – anti N-glycolyl (lung carcinoma, breast carcinoma, melanoma) [41] • Tergenpumatucel-L (lung carcinoma) [42]
Modulate T-cell function	• CD137 agonism [43] • CD40 agonism [44] • CTLA-4 inhibition [45] • LAG-3 inhibition [46] • OX-40 agonism [47] • PD-1 inhibition [48] • PD-L1 inhibition [49] • PD-L2 inhibition [50,51]
Oncolytic viruses	• Talimogene laherparepvec (T-VEC, melanoma) [52]

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