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Review

Radiotherapy and immune checkpoints inhibitors for advanced melanoma

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ABSTRACT

Introduction: The therapeutic landscape of metastatic melanoma drastically changed after the introduction of targeted therapies and immunotherapy, in particular immune checkpoints inhibitors (ICI). In recent years, positive effects on the immune system associated to radiotherapy (RT) were discovered, and radiation has been tested in combination with ICI in both pre-clinical and clinical studies (many of them still ongoing). We here summarize the rationale and the preliminary clinical results of this approach.

Materials and methods: In the first part of this review article, redacted with narrative non-systematic methodology, we describe the clinical results of immune checkpoints blockade in melanoma as well as the biological basis for the combination of ICI with RT; in the second part, we systematically review scientific publications reporting on the clinical results of the combination of ICI and RT for advanced melanoma.

Results: The biological and mechanistic rationale behind the combination of ICI and radiation is well supported by several preclinical findings. Retrospective observational series and few prospective trials support the potential synergistic effect between radiation and ICI for metastatic melanoma.

Conclusion: RT may potentiate anti-melanoma activity of ICI by enhancing response on both target and non-target lesions. Several prospective trials are ongoing with the aim of further exploring this combination in the clinical setting, hopefully confirming initial observations and opening a new therapeutic window for advanced melanoma patients.

The main role of the immune system is to restore normal tissues' homeostasis when altered by pathologic processes, including neoplastic transformation [1]. The immune system is often successful in eliminating neoplastic cells. Thus, all established tumours need to overcome immunity to progress and grow, and most of them successfully escape immune control, through different mechanisms [2,3]. Until recently, attempts in developing and applying immunotherapeutic strategies aimed to enhance innate and adaptive immune response failed in controlling most of solid tumours, with some exception represented by melanoma and renal cancer, where different forms of immunomodulation have been used for years. The clinical scenario drastically changed after the introduction of immune checkpoints inhibitors (ICI), a new class of targeted drugs able to activate the immune system against cancer cells, and showing efficacy for both solid tumours and haematological malignancies, with striking results leading to unexpected survival gains for advanced/unresectable melanoma [4]. Melanoma is actually the first cancer subtype where these immune-activating agents showed an advantage in survival over standard chemotherapy, and data from large clinical trials confirmed a substantial benefit with prolonged survival [5].

Over the last decade, it was also hypothesized that the combined effects of radiation therapy (RT) and immunotherapy in metastatic tumours might be synergistic, and this research field is currently one of the most stimulating and potentially practice-changing topics in radiation oncology. Several mechanisms have been proposed for explaining the interaction between RT and the immune system. Among them, microenvironment modification, cytokine and danger signals release, pro-inflammatory effect and immunogenic cell death pattern [6–8]; one of the most attractive experimental hypotheses is that ionizing radiations may act as an "in situ" vaccination in cancer patients, enhancing what has been called the "abscopal" effect after RT [9]. Such effect has been occasionally observed in patients undergoing palliative RT

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(especially in melanoma), and consists in a response of untreated (distant, outside radiation volumes) lesions following a radiation cycle to one lesion [10]. According to preclinical models, the "abscopal" effect is immune-mediated [9], and thus may be enhanced by the combined use of ionizing radiation and immune-modulating drugs of different classes, for example the immune checkpoint inhibitor ipilimumab, an anti-CTLA-4 monoclonal antibody which binds to T cells [11].

Ipilimumab activates T cells by blocking the inhibitory signal mediated by CTLA-4 through the interaction with surface receptors on antigen presenting cells (APC). Retrospective clinical reports showed that the combination of RT and ipilimumab was able to trigger the abscopal effect in a proportion of melanoma patients, and that this effect might prolong survival [12–14]. Additionally, experimental data provided the proof of principle that radiation and immunotherapy may favourably interact to enhance abscopal anti-tumour effects, and radiation may be used as a way to potentiate the effects of immunotherapy [15]. At the same time, new insights into the mechanisms leading to resistance to the combination of radiation and ICI and possible approaches for overcoming this phenomenon have been discovered [16]. As a consequence of the prolonged survival time achievable with new generation systemic therapies, RT to one or few metastatic sites (either in conventional fractionation or delivering high dose in few fractions) is now widely in use as a local therapy especially for oligo-metastatic disease [17].

Aim of this review is to focus on the potential therapeutic partnership between RT and ICI in advanced melanoma, discussing the most relevant pre-clinical and clinical findings, current research and future challenges.

Materials and methods

A narrative methodology was used for selecting and reporting studies on the clinical use of ICI for advanced melanoma, and for describing the biological and mechanistic basis of the combination of radiation and ICI. A systematic review was then performed according to validated guidelines [18,19] for selecting clinical studies reporting on the combination of RT and ICI for advanced melanoma. For this second part, we searched for English-language full length articles published from January 2000 to December 2015 using PubMed, and only studies reporting clinical outcomes following the combination of ICI and RT for metastatic melanoma were included. Studies were excluded if: (a) they were review articles and (b) they were not the most recently published outcomes, in instances of multiple publications from the same study cohort. The search strategy was "metastatic melanoma" OR "advanced melanoma" AND "radiotherapy" OR "radiosurgery" OR "stereotactic body radiotherapy" AND "ipilimumab" OR "pembrolizumab" OR "nivolumab", which identified 560 articles. Two clinicians reviewed these records to determine which were suitable for inclusion according to the pre-defined criteria, selecting 11 reports. Five more articles were added from reference lists of the selected publications, for a total of 16 reports on the clinical outcomes of the combined treatment.

Immune checkpoints inhibitors in melanoma: state of the art and new challenges

Until recently, the medical management of unresectable metastatic melanoma was based on the use of chemotherapy, either as single agent (dacarbazine, temozolomide or fotemustine) or multi-drug associations, with or without biotherapies such as interferon or interleukin-2. Despite the optimistic results coming from mainly single centre phase II trials suggesting a potential benefit of chemotherapy plus interferon and/or interleukin-2, a series of randomized trials did not demonstrate any advantage [20]. Two large meta-analyses clearly showed that even if bio-chemotherapy may increase the percentage of responses, this does not result in any improvement of survival, while is coupled with a higher toxicity [21,22]. The unsatisfactory results obtained by (bio)-chemotherapy were recently summarized in a study analysing the clinical data of more than 2000 patients enrolled onto 42 phase II trials since 1975. An overall 1-year survival of 25.5% and a median survival of 6.2 months were achieved, without any significant improvement over the last 30 years [23].

Even if it was well known that T-cell response is regulated through a complex balance of inhibitory and activating signals and that the tumour itself can deregulate these pathways leading therefore to an impairment of the immune system activities [3], the relevant new concept which was developed following the failure of cytokine-based immunotherapy was the potential of targeting these inhibitory and activating immunological synapses as a new tool to promote anti-melanoma immune response. Up till now, while the field is rapidly evolving and new drugs are under investigation, two main types of monoclonal antibodies targeting immune checkpoints have been developed and investigated in the treatment of metastatic melanoma. The first targets the cytotoxic T-lymphocyte antigen 4 CTLA-4, the other the Programmed Death 1 (PD-1) pathway. It is of relevance that both compounds physiologically interact with immunological checkpoints leading to inhibitory signals for T cells (priming and effector phases): the blockade of these pathways allows the release of the immune system brake thus fostering, maintaining and stimulating the T-cell response [24].

Anti-CTLA-4

Ipilimumab is a fully humanized monoclonal antibody that binds to CTLA-4, a receptor expressed on the T-cell surface that interacts with CD80 (B7-1) and CD86 (B7-2) on the Antigen-Presenting-Cells (APCs) and down regulates T-cell response. CTLA-4 blockade allows CD28 to bind to B7-1 receptors, leading to immune activation, IL-2 secretion, cytotoxic T-cells expansion and proliferation [25]. The interaction of ipilimumab with the immune system takes place in an early phase of the immune response involving "naive" T lymphocytes and the APCs. This mechanism of action explains the characteristics of the clinical activity as well as the common side effects of this drug, consisting of immune-mediated reactions developing more frequently in the skin, gastro-intestinal tract (mainly diarrhoea), liver and endocrinal glands. Moreover, it gives reason to the delayed occurrence of a relevant clinical response.

After pre-clinical data and pilot studies showing activity, a randomized phase II study compared different dose regimens in metastatic melanoma (0.3, 3 or 10 mg/kg IV every 3 weeks), showing that both 3 and 10 mg/kg induced optimal response, even if the latter dose was coupled with an increase in immune-related adverse effects (irAEs) [26]. In the first phase III trial, ipilimumab ± glycoprotein 100 peptide (gp100) vaccine was compared with gp100 vaccine monotherapy in patients with unresectable stage III or stage IV melanoma. Ipilimumab monotherapy significantly improved median overall survival (OS) compared with gp100 vaccine monotherapy (10.1 months vs. 6.4 months) [27]. In a second randomized phase III trial, the combination of ipilimumab (10 mg/kg) and dacarbazine (850 mg/sqm) resulted in significantly superior OS compared to dacarbazine (850 mg/sqm) plus placebo (11.2 months vs. 9.1 months) [28].

Notably, ipilimumab produced a plateau in survival curves: a recent pooled analysis of OS data for 1.861 patients enrolled in 10 prospective and 2 retrospective trials, with up to 10 years follow-up, showed that the survival curve began to plateau around

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