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MELANOMA IMMUNOTHERAPY SF – REVIEW

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Immunotherapy and radiotherapy in melanoma: a multidisciplinary comprehensive review

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ABSTRACT

Melanoma is an extremely aggressive tumor and is considered to be an extremely immunogenic tumor because compared to other cancers it usually presents a well-expressed lymphoid infiltration. The aim of this paper is to perform a multidisciplinary comprehensive review of the evidence available about the combination of radiotherapy and immunotherapy for melanoma. Radiation, in fact, can increase tumor antigens visibility and promote priming of T cells but can also exert immunosuppressive action on tumor microenvironment. Combining radiotherapy with immunotherapy provides an opportunity to increase immunostimulatory potential of radiation. We therefore provide the latest clinical evidence about radiobiological rationale, radiotherapy techniques, timing, and role both in advanced and systemic disease (with a special focus on ocular melanoma and brain, liver, and bone metastases) with a particular attention also in geriatric patients. The combination of immunotherapy and radiotherapy seems to be a safe therapeutic option, supported by a clear biological rationale, even though the available data confirm that radiotherapy is employed more for metastatic than for non-metastatic disease. Such a combination shows promising results in terms of survival outcomes; however, further studies, hopefully prospective, are needed to confirm such evidence.

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Introduction

Melanoma is an extremely aggressive tumor accounting for about 5% of all cancers and characterized by a variable incidence depending on geographical and racial factors; in the past years, there have been major biological therapeutic strategies investigated including the targeting of BRAF, MEK, and KIT inhibitors[1]. In particular, melanoma is considered to be an extremely immunogenic tumor because compared to other cancers it usually presents a well-expressed lymphoid infiltration.[2]

For this reason, several monoclonal antibodies inhibiting different targets including anti-programmed cell death protein 1 (PD-1), anti-programmed death ligand-1 (PDL-1), and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) have been studied.[3,4]

The aim of this paper is to perform a multidisciplinary comprehensive review of the evidence available about the combination of radiotherapy (RT) and immunotherapy (IT) for melanoma.

Radiobiological rationale

The response to IT depends on preexisting tumor infiltrate and may be improved by RT, which is able to activate an antitumor immune response. Moreover, IT has proven to synergize with radiation-induced immune activation and to convert the immunosuppressive microenvironment of a tumor into an in situ vaccine,[5] boosting the abscopal effect, which is defined as the clinical observation of tumor responses outside the irradiated field. Radiation causes an immunogenic cancer cell's death, resulting in release of damage-associated molecular pattern molecules (DAMP) such as adenosine triphosphate (ATP) and High Mobility Group Protein B1 (HMGB1) and in translocation on the cancer cell surface of the "eat me signal" calreticulin that promotes phagocytosis. Also, upregulation of MHC-I expression on the tumor surface increases tumor antigen presentation.[6] In the cytosol, radiation-induced DNA fragments lead to activation of the Stimulator of Interferon Genes (STING) that in turn upregulate interferon type I (IFN-I), activating innate and adaptive immune responses.[6] Radiation can increase tumor antigens visibility and promote priming of T cells but can also exert immunosuppressive action on tumor microenvironment. Combining RT with IT provides an opportunity to increase immunostimulatory potential of radiation, even though factors influencing the final balance in immunomodulation are mostly

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unknown. Clinical observations suggest a link with irradiated site and strategy of treatment combination.[6] Recent immunological data showed that RT results in immune system enhancement, and in particular, the role of dose per fraction is crucial: in fact, doses above 12–18 Gy induce exonuclease Trex1, which attenuates radiation-induced immunogenicity by degrading cytosolic DNA.[7]

Techniques: external beam radiotherapy, interventional radiotherapy, proton therapy

RT is rarely used to treat non-metastatic melanoma while it plays an important role in metastatic disease.[8] About 15% of patients with melanoma have metastatic disease at diagnosis or will develop metastatic disease during their illness.[9]

Many retrospective studies showed a significant median overall survival (OS) benefit in patients who received RT combined with IT compared to IT or RT alone.[10–13] The optimal timing and the toxicity profile for RT in this setting of anti-PD 1 therapy remain unknown, and clinical experience related with this combination is poor.[10–16] However, several retrospective studied showed a significant median OS benefit for patients who received IT after RT[10–16] or in combination[10] compared to patients receiving IT before or after 5 weeks from RT.[11,13–17] Treatment with stereotactic RT (SRS) as compared to external beam RT (EBRT) was also a statistically significant predictor of improved OS.[12,13] Finally, the side effect profile of patients receiving RT combined with did not appear to be different from that of patients receiving RT or IT alone.[11,13–17]

Proton beam therapy (PBT) is becoming an alternative to treat cancer patients undergoing RT. Preclinical and clinical data have shown potential immunosuppressive mechanisms associated with its dose distribution advantages. In vitro data has shown that PBT and X-ray irradiation achieves similar levels of survival of radiated melanoma cells. Still, only PBT induces long-term inhibition of migration of melanoma cells.[18] In vivo and clinical data for systemic tumor responses resulting from association of protons and IT are limited.[19]

Only a few clinical papers have been published about the association of interventional RT (IRT- brachytherapy) and IT. The potential advantages to IRT over EBRT may be the high conformal dose distribution and dose heterogeneity. The preclinical study demonstrated that IRT induces an antitumor immune response, thus enhancing IT.[20] Only three studies reported a combination of IRT and IT. Two of them implied 90 Y microspheres for liver metastases combined with either dual checkpoint blockade or a chimeric antigen receptor-modified T cell targeting the CEA antigen (NCT02913417, NCT02416466). In another paper, the authors investigate the addition of anti-PD-1 to standard chemoradiotherapy in patients with advanced cervical cancer (NCT02635360).

Timing: pre, concomitant, post

Traditionally, the timing sequence between chemotherapy (CT) and RT in solid tumors has been divided into sequential (either neoadjuvant or adjuvant) or concomitant, in particular, the rationale for administering concomitant CT is mainly to obtain a better local control enhancing the results of RT. On the contrary, when combining IT and RT, the primary rationale for such combination differs profoundly; in fact, RT administered triggers locally and fosters the immune system to obtain an enhanced systemic response.[21,22] When considering combination therapy in solid tumors including melanoma, several authors have proposed to use "induction" IT before CT; such a strategy may be appealing also for the combination of IT and RT.[23]

Concerning the combination of IT and RT, most clinical experiences present in literature show that such combination may be used before or after disease progression when the tumor has managed to escape the immune system or during the induction, within a few days before or after the first dose of IT.[24–30] For this reason, we may analyze the results of the current evidence dividing them into two main categories of timing combination:

(1) Combination of RT and IT after the tumor escapes the immune system or post-escape radiotherapy (PER); in this setting, there is no exact timing to define because the use of RT depends on the time of the tumor escaping the immune system surveillance.
(2) Combination of RT and IT during the induction phase or peri-induction radiotherapy (PIR); regarding this setting clinical experiences available in literature, there are both prospective and retrospective experiences as listed in Table 1 with irradiated sites classified according to AJCC 8th edition.[31]

As can be seen from Table 1, the vast majority of clinical data available in literature allows us to see how RT is employed more for metastatic than for non-metastatic disease; the main reason could be the fact usually surgery is the first choice of treatment for primary lesions except for selected clinical settings such as uveal melanoma.

Due to the radio-resistance of melanoma, very high doses are needed to obtain a complete remission; for this reason, the use of RT as alternative to surgery needs to be evaluated in multidisciplinary discussion considering the location and the treatment sequelae.

Locally advanced

Locally advanced melanoma includes unresectable stage IIIB, IIIC, and IVM1a.[32,33] Several local treatments are effective for unresectable locally advanced melanoma.[34] Nevertheless, data about the combination of immune checkpoint inhibitors and RT for locally advanced melanoma are limited.

Theurich et al. conducted a retrospective clinical study to test the efficacy of the combination of local tumor treatment (RT or electrochemotherapy or selective internal RT) and ipilimumab in 45 advanced melanoma patients, 8 of them (17.7%) with stage IIIC disease and 6 (13.3%) with stage IVM1A.[35] Considering the subjects without central nervous system metastases, OS was 117 weeks for patients treated with ipilimumab and local treatment versus 46 weeks with ipilimumab alone (HR 0.41; 95% CI, 0.17–0.78, $p = .0116$). The addiction of radiation therapy to ipilimumab allowed a better outcome irrespective of locally advanced (stage IIIC+IVM1a) or distant organ metastatic disease (stage IVM1b+c) at multivariate analysis (HR 0.57, 95% CI 0.23–1.41, $p = .23$).[35] Another retrospective study considered

Table 1. Summary of main studies available in literature about PIR in melanoma.

Author	Year	Type of study	Drug used	PIR	Median induction to PIR time	Dose and fractionation	Principal metastatic irradiated site
Barker et al.	2013	Retrospective	Ipilimumab	18 patients	Between 0 and +16 weeks	30 Gy in 10 fx	M1c
Twyman-Saint Victor et al.	2015	Prospective	Ipilimumab	22 patients	Between 0 and +5 days	From 12 Gy in 2 fx to 24 Gy in 3 fx	M1b
Chandra et al.	2015	Retrospective	Ipilimumab	47 patients	Between 0 and +28 days	30 Gy in 10 fx	M1a and M1d
Hiniker et al.	2016	Prospective	Ipilimumab	22 patients	Between 0 and +5 days	From 18 Gy in 1 fx to 50 Gy in 4 fx	M1b and M1c
Liniker et al.	2016	Retrospective	Nivolumab or pembrolizumab	27 patients	Between −11 and +7 days	30 Gy in 10 fx	M1a and M1d
Kato et al.	2019	Retrospective	Nivolumab or pembrolizumab	4 patients	Between −54 and 0 days	From 18 Gy in 1 fx to 50 Gy in 25 fx	M1d
Kim et al.	2019	Retrospective	Pembrolizumab	11 patients	Between −9 and 0 days	Median 36 Gy (range 20–60) and median fraction 5 Gy (range 1.8–8)	M1a

patients treated with peri-induction radiotherapy (PIR) and ipilimumab.[26] Among the 29 patients who underwent RT between the first and the last dose of ipilimumab, 3 had unresectable M0 or M1a disease. PIR and ipilimumab did not cause unexpected rate of adverse events or detrimental effect on ipilimumab-induced survival benefit.

In a phase II trial, stereotactic body radiation therapy was performed after the first nivolumab administration in 20 advanced melanoma patients.[36] This trial enrolled seven patients (35%) with locally advanced disease. The overall response rate of 45% was similar to that obtained with nivolumab alone in the historical controls, excluding an abscopal effect in these patients' population. Prospective trials are warranted to establish the role of the combination of RT and IT for locally advanced melanoma. Two phase I (NCT01557114 and NCT01996202) and one phase II (NCT01689974) prospective studies considered locally advanced melanoma patients treated with the combination of ipilimumab and radiation therapy. All these studies completed the enrollment period. The results will provide further data on safety and efficacy of immuno-radiation for locally advanced melanoma patients.

Systemic disease

Brain metastases

Brain metastases occur with an incidence of 10–40% in advanced stage melanoma[37] and are associated with significant morbidity and account for 20–54% of reported deaths from melanoma.[38] The standard of care remains the resection of large symptomatic lesions or the RT, followed by systemic therapy. SRT allows for a local control (LC) rate up to 90% and a median OS of 5–11 months.[39,40] Recently, with the introduction of ipilimumab, the interest about the synergistic effect has increased. Local RT can increase the permeability of the blood–brain barrier,[41] can prime antitumor immunity through release of tumor antigens,[42] and alter the tumor proinflammatory microenvironment.[43] Unfortunately, results are often contradictory. Some studies have reported the benefit of OS or LC in patients who receive ipilimumab and RT,[11,17,44–47] with a prognosis becoming at least similar to that of patients without brain metastaes. Some other studies have shown no difference in terms of LC or OS,[12,48] and others reported a survival benefit in case of SRT before ipilimumab.[14,16] Regarding the toxicity, several authors did not observe an increase of radiation necrosis, hemorrhage, or other toxicity in cases of combination of RT with IT.[9,11,12,16,44,48]

Liver metastases

The frequency of liver metastases in patients who present with stage IV melanoma disease is 15–20%, with a 5-year survival of less than 10%.[49] Several studies have reported evidence of the immunogenic effect with local irradiation of liver metastases who receive immune checkpoint inhibitors (ICIs).[35,50,51] The efficacy of PIR and ipilimumab in metastatic melanoma on OS outcomes has been reported in prospective and retrospective studies, with a median OS of 19 months (4–39 months).[26] Immune-related-adverse events (ir-AEs) were similar to those

produces by use of ipilimumab alone.[52] Also, the combination between anti PD-L1 and RT would seem to be effective and safe.[53] The best dose/fractionation regimen is still a matter of debate. Patients receiving a higher dose-per-fraction (>3/5 Gy/fx) have shown better clinical outcomes.[54] Concerning the timing, sequencing, and interval, some authors did not identify a significant difference in the rates of ir-AEs.[52,53] Although the toxicity increase could be associated to the temporal proximity of the two treatments.[52] Gabani et al.[55] observed that the addition of SBRT to ICIs improved OS in patients with soft tissue metastases at least 30 days before starting IT. However, very few liver melanoma metastatic patients have been included in these studies. Future clinical trials should consider the site, the IT agents, and the timing of RT to select patients who could benefit from their synergy.

Bone metastases

Bone metastases are a common site of melanoma metastatic spread after lung, liver, and brain, occuring in about 5–15% of patients[49,56,57] with a prevalent involvement of the axial skeleton. The prognosis is poor and almost similar to that of patients developing brain or liver metastases. Five-year survival is approximately 27%[58] with a median survival of 10.7 months.[59] Worst prognosis factors for survival are male patients, melanoma of the trunk, high LDH levels at bone meatstases diagnosis, evidence of ≥3 metastatic sites as well as ≥5 bone meatstases.[59] Bone meatstases can cause severe and debilitating effects including pain, spinal cord compression, hypercalcemia, and pathological fracture. RT provides symptomatic improvement of 50–86% patients[60–63] and response improves with total doses of 30 Gy.[64–66] Since the RT plays a role in the palliative treatment of metastatic disease, its use in combination with IT has been explored,[44,55,67,68] indicating a possible improvement in clinical outcomes.[35,60,69] RT dose and fractionation may also play an important role in maximizing induction of immune response[24,70] even if confirmation of survival benefit from large prospective studies is lacking.[25] Analysis of retrospective large database on the patterns of care of patients with bone meatstases receiving IT highlights a better survival with the integration of palliative RT to IT (16 months, 95% CI = 10.4–20.7);[59] furthermore, the combination of hypofractionated RT (>5 Gy/fx) and IT demonstrated a significantly higher survival probably due to its immunogenic effect.[60,71,72]

In these recent years, IT's introduction has changed the natural history of melanoma and its therapeutic landscape with a greater proportion of oligometastatic presentation theoretically suitable for SBRT[72] to improve the therapeutic ratio through increased tumor cell killing while maintaining stable or decreased toxicity.[52,73–75]

A more significant number of fractions and a generally larger area of treatment with CFRT (≤5 Gy/fx) may lead to more substantial lymphopenia, which can hinder tumor cell eradication by cytotoxic T lymphocytes,[76–78] and this could partially justify a little benefit from the combination with IT.[59]

Some factors that could influence treatment outcomes have yet to be identified in future clinical trial incorporating RT for BM, such as the best temporal sequencing of RT/IT, and which RT dose-fractionation would be more "immunogenic."

Ocular melanoma

Melanoma of the ocular region comprises about 5% of all patients with melanoma and includes conjunctival melanoma and uveal melanoma; these subtypes of ocular melanoma have distinct biological features, which should be taken into consideration when making treatment decisions.[79] The tumor mutational burden is hypothesized to correlate with the neoantigen load and thus the immunogenicity of tumors. Currently, it seems to be a useful predictive biomarker for response to ICIs across tumor entities.[80] While conjunctival melanomas, as well as cutaneous, are associated with ultraviolet sun exposure and display a subsequent extremely high mutational burden with up to 100 mutation per megabase,[81] in uveal melanoma the mutational load is among the lowest of all cancer types of around 0.5 per Mb sequence.[80,82] In fact, uveal melanoma arises in the eye in an immune-privileged environment that possesses inhibitory properties against both the innate and the adaptive immunity system.[83] This may protect cancer cells not only at the site of the primary tumor but also may hamper a successful antitumor immune response in other sites of the body and thus contribute to ICIs blockade failure in uveal melanoma.[84] For local treatment, IRT with plaques and PBT, represent the gold standard of care; however, RT has not yet been associated to IT, even in the presence of negative prognostic factors, because the biological characteristics of UM do not justify a combination of RT with IT at the moment.

The management of metastatic uveal melanoma is challenging. Although it is characterized by some immune infiltrates, the use of ICIs for metastases has shown limited response in comparison to cutaneous melanoma.[85] Recently, an exceptional immune response in UM patients harboring MBD4 mutations has been described. This evidence of selected groups of UM that could benefit from IT[86] in addition to RT or CT aimed at modulating and enhancing the antitumoral immune response in uveal melanoma opens new perspectives for the future. Wide surgical excision followed by cryotherapy to the surgical margins is the first-line treatment for conjunctival melanoma, supplemented with topical chemotherapy or local RT due to the high recurrence rates.[87] Adjuvant RT treatments include EBRT, PBT, and IRT. Despite local adjuvant treatment, the risk of local recurrence is high (30–60%), nodal involvement occurs in 15% of patients, and finally about 20–30% of patients develop distant metastases.[79] Given genetic similarities to cutaneous melanoma, in a few case reports/case series, immune-based therapies have shown durable responses to treatment after excision and adjuvant RT, in locally advanced or metastatic conjunctival melanoma.[88,89] While clinical trials for cutaneous melanoma and few studies for mucosal melanoma have reported the results of combined RT and anti-PD-1 therapy, because of its rarity no study has been conducted to compare the role of RT with IT versus RT alone, in the adjuvant treatment of conjunctival melanoma.

Elderly patients: clinical management

The rapid expansion of the aging population is associated with an increase in skin cancer and melanoma incidence. This scenario represents one of the most significant challenges in the management of this cancer.[90] On the one hand, it is increasingly crucial

for the effective treatment of melanoma.[91] On the other hand, aging is associated with a dysregulation of the immune system (immunosenescence and inflammaging), which could alter the effectiveness of the treatments themselves.[92–94] It is in the older cancer patient that the real personalization of treatments takes place. Factors related to the patient him/herself rather than cancer must be considered in the therapeutic choice. Compliance linked to the social network, polypharmacy, multimorbidity, frailty, active life expectancy, and the physiological changes related to aging are the main factors to consider when choosing treatment in the elderly patient.[95–98] Older cancer patients often do not have a social network able to cover the indications or problems relating to treatments. In these cases, it is important to avoid starting a treatment that patients may not complete due to external factors. There is need for a shift of mindset from the idea of comorbidities (as the presence of multiple pathologies in addition to the main one) to the holistic idea of several diseases present (acute and chronic) in the patient, each of which is able to influence the others and the prognosis in the patient. Frailty, the basis of modern geriatrics, is the concept of a homeostatic mechanism for which a frail patient, if subjected to stress (such as cancer treatments), can precipitate in a state of disability. Therefore, it is essential to identify the frail patient from the fit one before making any therapeutic choice. Hypothesize an assessment of the sarcopenia, closely linked to more significant toxicity to treatments, and customize therapies based on these data.[99] For active life expectancy, any treatment choice in the older patient should consider the patient's life expectancy and quality of life. These two factors are not related to the chronological age data but rather to the patient's physical and cognitive performance.[96]

Finally, it is necessary to remember that physiologically the body has changes related to aging that impact drugs' pharmacodynamics and pharmacokinetics.[97] Thus, before any decision, it is essential to carry out a geriatric assessment of the patient (through a screening test or a comprehensive geriatric assessment) in order to be able to carry out a truly personalized treatment.

Conclusions

The combination of IT and RT seems to be a safe therapeutic option, supported by a clear biological rationale, even though the available data confirm that RT is employed more for metastatic than for non-metastatic disease. Such a combination shows promising results in terms of survival outcomes; however, further studies, hopefully prospective, are needed to confirm such evidence.

Disclosure of potential conflicts of interest

All authors declare no potential conflicts of interest.

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