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EDITORIAL

Editorial of special focus on melanoma immunotherapy

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Immune checkpoint inhibitors (ICIs) dramatically improved the survival of patients affected by melanoma during the last years. Therefore, immunotherapy currently represents a milestone of treatment for this disease.[1]

The wide use of this therapeutical option raised new issues. Purpose of this focus was to take a picture of current role and future directions of immunotherapy in melanoma.

After the demonstration of efficacy in metastatic disease, ICIs have been employed in adjuvant setting. Clinical trials demonstrated the advantage of anti-PD-1 therapy in terms of relapse-free survival, after radical resection of melanoma. Nevertheless, the role of adjuvant immunotherapy in some subgroups of patients remains challenging: stage IIIA, patients with microsatellite only without nodal involvement, BRAF-mutant melanoma.

The meta-analysis conducted by Bersanelli included 3043 patients enrolled in clinical trials investigating immunotherapy in radically resected stage III–IV melanoma. This analysis confirmed the relapse-free survival benefit of anti-PD-1 compared to anti-CTLA-4/placebo. The advantage has been shown regardless sex, age, BRAF status, PD-L1 expression, and ulceration, whereas the benefit was not significant for stage IIIA according to AJCC 7th ed. (available in only two of all the analyzed studies) and stage M1c (a small sample size across the trials was identified). The authors suggested as possible directions in the adjuvant setting the prolongation of therapy over 1 year in resected stage IV melanoma and the combined anti-PD-1/anti-CTLA-4 therapy in selected high-risk patients. They also underlined the lack of data regarding subjects with only sentinel biopsy positivity (without radical lymph node dissection), who represent an increasing proportion of patients in daily practice.[2]

With regards to adjuvant treatment, immunotherapy demonstrated interesting results also in earlier stage of disease.[3,4]

ICIs improved relapse-free survival when employed in adjuvant setting. Nevertheless, a proportion of stage III melanoma patients relapse despite immunotherapy used after radical resection.

This represented the assumption for clinical trials testing ICIs as neoadjuvant therapy in stage III melanoma. In fact, this type of treatment could stimulate antitumor immunity by activating antigen-specific T cells in the primary site; in this way, the activated immune system could be able to avoid the relapse after radical resection of melanoma. Combination of anti-PD-1 and anti-CTLA-4 antibodies showed a higher complete response rate than the same agents alone. The role of shorter schedules or with a better tolerability, the impact of the adjuvant therapy and the importance of surgery on lymph node basin should be completely elucidated.[5]

The complete response may be considered a promising surrogate marker of relapse-free survival. In addition, it can be a parameter of sensitivity to a specific therapy, guiding future choices of treatment. Therefore, the identification of biomarkers of response is a crucial medical need. These factors could also avoid toxicity in patients who cannot benefit from a neoadjuvant approach. Among the possible biomarkers, PD-L1 is one of the most studied but it cannot be reliably considered predictive of response. Several other factors have been evaluated but they use have not yet been validated.[6]

A lot of treatment options have been considered in neoadjuvant/adjuvant setting as well as in metastatic melanoma. Among them, several studies have been conducted and further trials are ongoing with combination therapies, including a wide variety of agents, and intralesional treatments.

One of the benefits of combination therapies is that they are more likely to overcome drug resistance. Furthermore, a simultaneous use of immunological agents can allow to enhance the immune response against neoantigens released in tumor microenvironment.

The efficacy of combination therapy was particularly remarkable for the treatment of brain metastases, as reported by trials investigating anti-CTLA-4 and anti-PD-1.[7]

Among all the treatment options, intralesional therapies are one of the most intriguing approach.[8] The skin was considered the best site for the application of this treatment modality, because of the simple way of administration. In addition, intratumoral therapies represent an "in situ vaccine," potentially able to exert an immune response with local and systemic disease control.

To date, in clinical studies we have not yet observed a greater efficacy of intratumoral therapies compared to systemic therapies. Nevertheless, the association of this approach together with systemic therapies (i.e. checkpoint inhibitors) represent a promising strategy, supported by a strong biological rationale.

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Similarly, radiotherapy is able to elicit an immune stimulation and could act synergistically with immune-checkpoint inhibitors. This association seems to be safe but prospective trials are needed to investigate the additional benefit which can be obtained combining radiotherapy to immunotherapy.[9]

During the last years, particular attention has been dedicated to the role of gut microbiota in the response to immunotherapy and in occurrence of side effects. Preclinical studies suggest that intestinal microbiota can influence the efficacy of immunotherapy. Trials will allow us to definitively know whether the manipulation of microbiota can increase the efficacy of immunotherapy.[10]

Alongside all the strategies aimed at maximizing the efficacy of immunotherapy, it is also very relevant to consider the immunotherapy toxicity profile. The proper management of side effects can avoid treatment discontinuation, ensuring an adequate drug exposure.

The possibility of a new spectrum of immune-related adverse events should be taken into account during immunotherapy. The cutaneous reactions, for example, which represent some of the most common adverse events, include specific dermatologic entities. Maculopapular rash, psoriasiform and lichenoid eruptions can be observed; they are usually mild, but it can be also severe.[11]

The efficacy of immune-checkpoint inhibitors differs between different types of melanoma. It is well known the limited efficacy of immunotherapy in uveal melanoma.

Nevertheless, the immune system seems to play a crucial role also in this disease. In an exploratory study, the circulating immune profile predicts the survival of uveal melanoma patients. Serum immune-checkpoint inhibitors together with cytokines/chemokines can identify patients with poor prognosis despite immunotherapy and patients with long survival treated with an anti-PD-1 agent. The study also demonstrated a different circulating immune profile of uveal melanoma compared to cutaneous melanoma during anti-PD-1 therapy, reflecting the discrepancy in efficacy of immune checkpoint inhibitors.[12]

In recent years, immunotherapy has allowed exciting results in melanoma. Further efforts are still needed to understand the mechanisms underlying the action of these agents. Predictive factors of toxicity or response and markers of resistance can help to establish a more personalized therapeutic strategy. Clinical trials in near future will have to include treatments based on specific molecular/immunological features.

Much has been achieved with immunotherapy in melanoma, much more has to be done.

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