Title of Research
Cutaneous Toxicities Associated with Immune Checkpoint Inhibitors in Advanced Melanoma: A Systematic Review and New Proposed Management Algorithm

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Summary of Research
The emergence of immune checkpoint inhibitors (ICI) for solid tumours represents a major advance in cancer therapeutics and has demonstrated promising antitumor effects as well as significant survival benefits in a range of solid malignancies. Treatment with immune checkpoint inhibitors is associated with tissue-specific inflammatory responses termed immune related adverse events (irAE). Dermatologic immune-related adverse events are the most frequent immune-related adverse events in trials of patients with melanoma. A wide spectrum of cutaneous toxicities have been reported, ranging from mild self-limiting rash and/or pruritus to life-threatening cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Interestingly, induction of certain immune-related adverse events, including vitiligo, have been historically suggested as a positive prognostic factor in patients treated with immunotherapy, but this has yet to be firmly established in immune checkpoint blockade. IrAE are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) classification. Specific toxicity management guidelines have been developed to mitigate irAE from ICI therapy and have become standard of care in melanoma and renal, lung and urothelial carcinomas. Treatment is escalated according to severity of the grading. The appropriateness of this grading system for irAE has not been evaluated.

In this study, the research team will review the spectrum of skin toxicities encountered with immune checkpoint inhibitors and critically assess how they impact a patient's treatment and outcome. They propose to do this by conducting a thorough review of all of the clinical trials using immune checkpoint inhibitors in patients with melanoma that has spread. By reviewing the data relating to each individual patient, they will have a wealth of previously unreported data assessing how this toxicity was graded and managed based on the current grading system. They will further assess how this might have impacted the patients' treatment and outcome.

The researchers believe that combining these data with their expertise in managing skin adverse effects in this context would set the foundation for presenting a more nuanced grading system, specifically designed for patients receiving these treatments. Their aim would be that this revised classification system would improve the management of these common complications and maximize the benefit accrued from these life-prolonging immunologic therapies.

Study Design

The researchers wish to evaluate dermatological toxicities encountered during ICI therapy in metastatic melanoma patients. They propose to do this by conducting a systematic review and meta-analysis with the aim of comprehensively characterizing the spectrum of cutaneous toxicities encountered with these agents. They will describe the dermatological toxicities and attempt to critically analyze how these toxicities impact the treatment pathway, including treatment delays/discontinuations as well the potential correlation of cutaneous adverse events with improved outcomes. Based on this body of evidence, they will critically evaluate the suitability of the current CTCAE classification of cutaneous toxicities for ICI therapy and present a revised classification and treatment algorithm.

The researchers hypothesize that large-scale analyses of toxicity data from well-designed trials using ipilimumab and/or nivolumab in advanced melanoma will reveal that cutaneous toxicities generally occur early on in the treatment pathway and although common, have minimal serious adverse impact on the underlying anticancer treatment pathway (as evidenced by withdrawals/ deaths due to cutaneous toxicity). They envisage that there will be wide heterogeneity in the way cutaneous toxicities are graded, recorded, investigated and managed and that current CTCAE grading criteria do not adequately account for the spectra of toxicities encountered in this clinical context. The researchers strongly believe that with a more nuanced approach to grading and classification (particularly drawing on experience from well-established existing dermatologic classifications), a significant proportion of immune checkpoint inhibitor-related cutaneous toxicities could be more accurately graded. This might ultimately lead to fewer treatment withdrawals/interruptions as well as a more reserved use of supportive high-dose systemic immunosuppressive therapies. Lastly, they hypothesize that careful analysis of the individual patient data using the multivariable Cox model will reveal that the special case of immune checkpoint inhibitor-related depigmentation/vitiligo will be positively correlated with improved survival.

The primary endpoint will be physician-reported treatment-related cutaneous AEs of any grade, measured according to the CTCAE in clinical trials of ipilimumab, nivolumab or ipilimumab combined with nivolumab in advanced melanoma.

Secondary endpoints will be the: proportion of participants requiring systemic immunosuppressive therapy to manage immune-checkpoint inhibitor related cutaneous

toxicities; median duration of interruption of therapy as a consequence of cutaneous toxicities; proportion of participants withdrawing from immune checkpoint inhibitor therapy due to cutaneous toxicities; progression free and overall survival following immune checkpoint inhibitor therapy in the presence/absence of skin-related AEs; and a qualitative analysis of the correlation between documented nature/grade of toxicity to that objectively assessed from pictorial/biopsy evidence (where available).

Study Population

The patient population will be adults with American Joint Committee on Cancer (AJCC) Stage IV or inoperable stage III cutaneous melanoma enrolled onto a BMS trial of ipilimumab, nivolumab or the combination of these agents. Studies administering these agents in any line of therapy will be considered; however, only data for doses taken into expansion phase II or phase III trials will be evaluated. Regimens where ICI is combined with other active systemic/locoregional therapies (including cytotoxic chemotherapy, targeted therapy, other forms of immunotherapy, radiotherapy) will be excluded. However, where available, data from the ICI-only arms of these trials will be extracted. Only completed and fully reported trials (either in publication or abstract form) will be included. Patient level data from published BMS trials of the above agents at their licensed doses will be requested.

Funding Source of Research

This study will be funded by the Addenbrookes Charitable Trust (ACT).

Requested Study

CA184-002 (MDX010-020)-NCT00094653: MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDX-010/MDX-1379 Combination Treatment for Patients With Unresectable or Metastatic Melanoma

CA184-042 (NCT00623766): Evaluation of Tumor Response to Ipilimumab in the Treatment of Melanoma With Brain Metastases

CA184-008 (NCT00289627): A Single Arm Study of Ipilimumab Monotherapy in Patients With Previously Treated Unresectable Stage III or IV Melanoma

CA184-240 (NCT01673854): Phase II Safety Study of Vemurafenib Followed by Ipilimumab in Subjects With V600 BRAF Mutated Advanced Melanoma

CA184-022 (NCT00289640): Study of Ipilimumab (MDX-010) Monotherapy in Patients With Previously Treated Unresectable Stage III or IV Melanoma

CA184-396 (NCT01990859): Phase 2 Study of Ipilimumab in Japanese Advanced Melanoma Patients

CA184-243 (NCT01709162): Study to Compare the Effect of Ipilimumab Retreatment With That of Chemotherapy in Advanced Melanoma

CA184-013 (NCT00050102): Comparison Study of MDX-010 (CTLA-4) Alone and Combined With DTIC in the Treatment of Metastatic Melanoma

CA184-007 (NCT00135408): A Study of MDX-010 (BMS-734016) Administered With or Without Prophylactic Oral Budesonide

CA184-004 (NCT00261365): Phase II Study to Determine Predictive Markers of Response to BMS-734016 (MDX-010)