British Association of Dermatologists Elective Prize/Project Grant – Summer 2019

A short report on a research project investigating dermatological drug reactions following immune checkpoint inhibition therapy for advanced melanoma

Robin Wang
The Royal London Hospital, London

977 words excl. acknowledgements + references

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Introduction
I spent 4 weeks of my summer elective in The Royal London dermatology department collecting patient data on dermatological drug reactions for all patients who had been documented to have received immune checkpoint inhibitors pembrolizumab, ipilimumab and nivolumab.

These monoclonal antibodies target inhibitory receptors (also known as immune checkpoints) including the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1), that limit T cell effectiveness in the setting of chronic inflammation, and have subsequently been implicated in melanoma progression and poor patient prognosis. Current data regarding cutaneous toxicity is limited and this project set out to elucidate the nature and frequency of dermatological reaction as an adverse effect to treatment for malignant melanoma. [1]

Method
Data was collected from a list of 184 unique patients from the hospital Powerchart and EPR software. All patients with a positive dermatological reaction i.e. any mention of a rash, vitiligo or blisters were included into an excel table. Isolated recordings of pruritis, as well as non-dermatological adverse effects were excluded. Our group was also particularly interested in bullous dermatoses as a consequence of immunotherapy, and as a result a separate table was compiled of just these reactions.

Recorded patient parameters for those included were as follows: age, sex, type of melanoma, site, date of diagnosis, staging, Breslow thickness, BRAF status, previous targeted therapy, metastasis status and location, type of immunotherapy commenced, start date, total cycles of therapy, cycles before the onset of reaction, other immunotherapy used, description of reaction, site, skin diagnosis, date of onset, months of therapy until onset, histology, treatment received – topical steroids, other topicals, systemic steroids, whether therapy was stopped during treatment, any other treatment, resolution status, status at last clinic visit, outcome, past medical history, family history.

Results
In total, 49 patients (26.7%) had significant reactions and were included in the final results table and subsequent analysis. 9 were on only ipilimumab, 16 on ipilimumab/nivolumab and 24 on pembrolizumab. Ipilimumab monotherapy had the highest proportion of reactions (45%) compared to Pembrolizumab which had the lowest (19.7%). The most common type of melanoma was ocular (n=20). The mean depth was 5.2cm. 14 patients had a positively documented BRAF mutation. The most common place of metastasis was the liver (n=28). The

most common reaction was a grade 1 pruritic rash (n=32). A total of 5 bullous reactions were recorded, all of which with corresponding histological biopsy report.

The most frequent location of rash was on the lower limb (n=15), followed by the upper limb (n=14). The mean total cycles of immunotherapy before onset was as follows: Pembrolizumab = 10.9, Ipilimumab =1.9, Ipi/Nivo = 1.9, with a combined mean of 6.3 cycles. The mean total months of immunotherapy before onset was as follows: Pembrolizumab = 7.5, Ipilimumab = 1.2, Ipi/Nivo = 1.4., with a combined mean of 4.3 months.

Of the 49 patients, 43 received some form of treatment for their reaction. The most frequently used topical steroid was Dermovate (n=15). The most frequent other topical was emollient therapy (n=12). 8 patients in total required systemic steroid therapy (either prednisolone (n=6) or methylprednisolone (n=2)). 21 patients received oral antihistamines. 9 patients had to stop immunotherapy due to the severity of their reaction.

In 33 patients the rash resolved with treatment without having to stop immunotherapy. In 8 patients the rash resolved only after stopping immunotherapy. In 2 patients the rash did not resolve at all. Of the 49 patients, 14 cleared their melanoma, 16 had ongoing disease, 6 were in palliative care, 11 had died and 2 had an unclear outcome. Patients on Pembrolizumab had the highest rates of disease clearance (41.7%) and the lowest mortality rates (16.7%).

Discussion

The current understanding of adverse events secondary to immune checkpoint inhibition therapy is that they arise as a result of persistent T-cell mediation immune stimulation, and as a result naturally manifest in the form of colitis, hepatitis, thyroiditis, as well as immune-related dermatological toxicity in the form of a maculopapular rash, lichenoid reactions and vitiligo. [2]

These results are consistent with current data regarding the incidence of rash: one meta-analysis indicates an overall incidence of skin rash in patients on ipilimumab of 24.3%, with my data indicating a rate of 26.7%. this reinforces the notion that dermatological immune related adverse events are extremely frequent in patients undergoing immunotherapy.[3] While the majority of patients will experience mild quality of life disruption, we found a few significant cases of bullous pemphigoid as well as widespread grade 3 maculopapular rashes that are relevant to add to the current knowledge on the toxicity profile of such a new therapeutic agent.

An interesting result is that the patients on Pembrolizumab encountered lowest frequency of adverse reaction as well as the highest rates of survival. This may be due to unobserved factors such as severity of disease/metastasis or the inclusion criteria for which immunotherapy was most suited to the patient's disease profile.

A notable drawback of my data collection was the difficulty in finding all of the recorded parameters in just the electronic patient data, resulting in many sections which had to have 'not documented' as an input, potentially affecting the ultimate analysis. I did my best to overcome this by trying to be thorough in my data collection, as well as clearly documenting when certain data was unobtainable.

Conclusion

In conclusion, of the total 184 patients, the observed rate of dermatological immune related adverse event was documented in my project as 26.7% (n=49), with a rate of bullous dermatoses as 2.7% (n=5). Further research with larger samples is needed to accurately portray more accurate rates of the less frequent complications such as bullous reactions and vitiligo.

I am incredibly grateful to have been given the opportunity to partake in this project. I have learned a lot and hope to pursue the project further with a poster presentation and hopefully publication of the data subsets.

References

[1] J. A. Seidel, A. Otsuka, and K. Kabashima, "Anti-PD-1 and Anti-CTLA-4 Therapies in Cancer: Mechanisms of Action, Efficacy, and Limitations," *Front. Oncol.*, 2018.

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