Targeted review of adverse events associated with treatments for stage 3 and 4 melanoma

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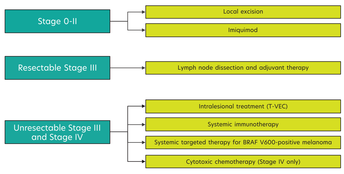
Background

Melanoma is the fifth most common cancer in the UK, with 15,906 new cases registered across the UK in 2015.[1]

The treatment of melanoma varies depending on the stage of the disease (Figure 1).[2]

Figure 1: NICE melanoma treatment pathway



Abbreviations: T-VEC, talimogene laherparepvec

Immunotherapy and targeted therapy have become standard treatments for patients with stage 3 and 4 melanoma, with chemotherapy now mostly reserved for when other treatments have proved ineffective.[3]

Despite their efficacy, all therapies are associated with adverse events (AEs).

Studies have shown that treatment-related AEs in patients with metastatic melanoma are associated with significant negative impacts on patients' quality of life, and their management is associated with substantial healthcare resource-utilization and related costs.[4-6]

Data published on AEs associated with these treatments have not been compared over the past five years.

Study objectives

The study aimed to identify and compare the most frequently reported AEs associated with chemotherapies, immunotherapies, and targeted therapies in stage 3 and 4 melanoma.

Methods

Targeted searches were conducted in the PubMed literature database to identify phase 3 studies published in the past five years (January 1, 2014 to December 31, 2018) that reported AEs associated with chemotherapies, immunotherapies and targeted therapies used in the treatment of stage 3 and 4 melanoma.

Study titles and abstracts were screened by two independent reviewers.

Study design details and data on AEs by treatment were extracted.

The following treatments were considered:

- Dacarbazine plus placebo
- Dacarbazine plus selumetinib
- Ipilimumab
- Ipilimumab plus placebo
- Nivolumab
- Nivolumab plus placebo
- Nivolumab plus ipilimumab
- Pembrolizumab
- Talimogene laherparepvec
- Dabrafenib plus placebo
- Dabrafenib plus trametinib
- Vemurafenib

AEs occurring in ≥10% of patients in any study group were recorded, in addition to grade ≥3 AEs occurring in ≥1% of patients.

Results

Twenty-six phase 3 studies[7-32] reporting AEs associated with chemotherapies, immunotherapies or targeted therapies used in the treatment of stage 3 and 4 melanoma were included; all categorized AEs by grade (e.g., all, 1-2, ≥3).

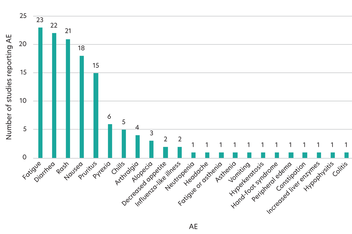
The all-grade and grade ≥3 AEs reported in the most studies were largely comparable (see Figures 2-3).

The most commonly reported all-grade and grade ≥3 AEs differed by therapy type:

- The all-grade AEs most commonly reported in studies of chemotherapies were diarrhea and fatigue, in studies of immunotherapies were diarrhea, fatigue and rash, and in studies of targeted therapies were fatigue and nausea (see Figures 4-6).
- The grade ≥3 AEs most commonly reported in studies of chemotherapies was neutropenia, in studies of immunotherapies was diarrhea, and in studies of targeted therapies was rash (see Figures 7-9).

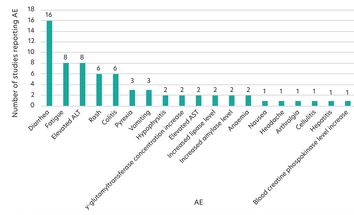
Note: findings from studies reporting AEs associated with chemotherapies are not included in Figure 3 to avoid double counting, as all the studies separated out grade ≥3 AEs into grade 3 and 4.

Figure 2: All-grade AEs reported across all treatments



Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

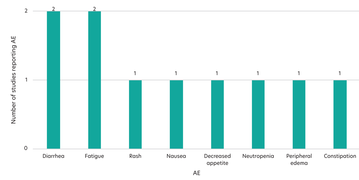
Figure 3: Grade ≥3 AEs reported in immunotherapies and targeted therapies



Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

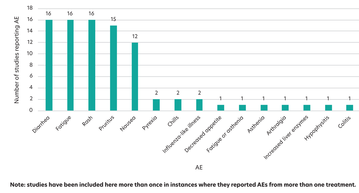
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Figure 4: All-grade AEs reported in chemotherapies



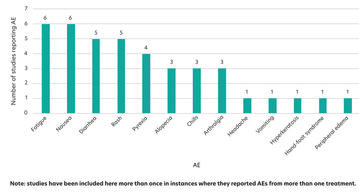
Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

Figure 5: All-grade AEs reported in immunotherapies



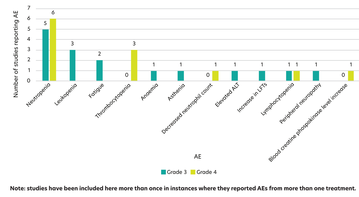
Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

Figure 6: All-grade AEs reported in targeted therapies



Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

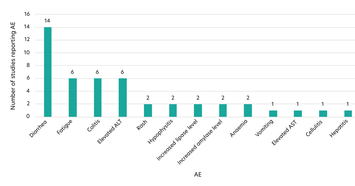
Figure 7: Grade ≥3 AEs reported in chemotherapies



Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

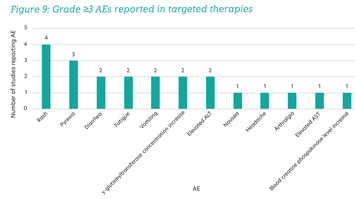
Figure 8: Grade ≥3 AEs reported in immunotherapies



Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Figure 9: Grade ≥3 AEs reported in targeted therapies



Note: studies have been included here more than once in instances where they reported AEs from more than one treatment.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase

Discussion

Data from the last five years show that chemotherapies, immunotherapies and targeted therapies used in the treatment of stage 3 and 4 melanoma are associated with high rates of AEs. There is therefore still substantial unmet need for therapies with improved safety profiles.

The most commonly reported all-grade and grade ≥3 AEs differed by therapy type.

Several approaches have been taken to further understand this unmet need. For example, Kartolo et al. (2018)[33] investigated predictors of immunotherapy-induced immune-related AEs (irAEs; including diarrhea and nausea) in a Canadian population, and found that factors such as sex, history of autoimmune disease, and steroid use before immunotherapy had statistically significant associations with irAE rates. However, further studies are required to evaluate the impact of steroids co-administered with immunotherapies.

Analysis of the Melanoma UK digital registry dataset[34] would allow verification of these early findings in the UK setting, and provide an understanding of predictors for immunotherapies with different mechanisms of action (e.g., CTLA-4 inhibitors [ipilimumab] and PD-1 inhibitors [nivolumab and pembrolizumab]).

Analysis of the Melanoma UK digital registry dataset may also provide insights on the impact treatment AEs have on patients' health-related quality of life, which up until now has not been adequately investigated.

Conclusions

Currently published data from clinical trials show that chemotherapies, immunotherapies and targeted therapies are associated with high rates of AEs.

Analysis of the Melanoma UK digital registry dataset would allow verification of these early findings the UK real world setting.

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