Adverse events associated with immunotherapies used in the treatment of stage 3 and 4 melanoma

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BACKGROUND

Melanoma

Melanoma is an aggressive form of skin cancer that originates from melanocytes in the basal layer of the epidermis.[1]

Melanoma is the fifth most common cancer in the UK, with 15,906 new cases registered across the UK in 2015.[2]

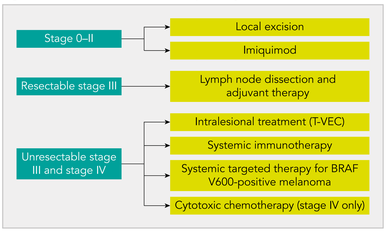
The incidence is rising, especially in older adults – just over half of melanoma cases each year are in people aged 65 years and over.[2]

However, melanoma also occurs relatively frequently in younger people (in contrast to most types of cancer): just under a third of melanomas in the UK between 2013 and 2015 were in patients aged younger than 50 years.[2]

Treatment guidelines

The treatment of melanoma varies depending on the stage of the disease (Figure 1).[3]

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.[4]

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

Studies have shown that the management of treatment-related AEs in patients with metastatic melanoma is associated with substantial healthcare resource utilization, high costs, and negative impacts on quality of life.[5–7]

Data published on AEs associated with immunotherapies have not been reviewed in a targeted way over the past five years.

Study objectives

The study aimed to identify the most frequently reported AEs associated with immunotherapies in the treatment of stage 3 and 4 melanoma.

METHODS

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

Study titles and abstracts were screened by two independent reviewers.

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

The following treatments were considered:

- Ipilimumab;
- Nivolumab;
- Pembrolizumab;
- Talimogene laherparepvec (T-VEC);
- Nivolumab plus ipilimumab.

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

RESULTS

Twelve phase 3 studies reporting AEs associated with immunotherapies used in the treatment of stage 3 and 4 melanoma were included (Table 1); all categorized AEs by grade (e.g., all, 1-2, ≥3).

The most frequently reported AEs across all grades were fatigue, diarrhea, pruritus, rash, and nausea (Figure 2).

Diarrhea, colitis, elevated alanine transaminase (ALT), and fatigue were the most frequently reported grade ≥3 AEs (Figure 3).

Certain all-grade AEs were associated with particular immunotherapies:

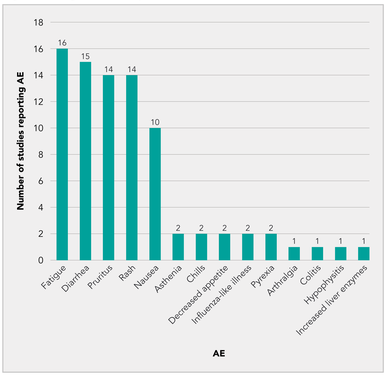
- Fatigue with T-VEC (50-51% of patients);
- Pruritus with ipilimumab (25-36% of patients);
- Diarrhea with nivolumab plus ipilimumab (44-45% of patients).

Table 1: Summary of findings from the literature

Study	Immunotherapies investigated	Top five all grade AEs occurring in ≥10% of patients	Top three grade ≥3 AEs occurring in ≥1% of patients
Eggermont *et al.* (2018)[8]	• Pembrolizumab	• Fatigue/asthenia (37%) • Diarrhea (19%) • Pruritus (17%) • Rash (16%) • Arthralgia (12%)	Not reported*
Robert *et al.* (2015)[9]	• Pembrolizumab • Ipilimumab	Pembrolizumab**: • Fatigue (21%) • Diarrhea (17%) • Rash (15%) • Pruritus (14%) • Asthenia (12%) Ipilimumab: • Pruritus (25%) • Diarrhea (23%) • Fatigue (15%) • Rash (15%)	Pembrolizumab: • Diarrhea (3%) • Colitis (1%) • Hepatitis (1%) Ipilimumab: • Colitis (7%) • Diarrhea (3%) • Hypophysitis (2%)
Schachter *et al.* (2017)[10]	• Pembrolizumab • Ipilimumab	Pembrolizumab**: • Fatigue (28%) • Pruritus (20%) • Diarrhea (19%) • Rash (16%) • Arthralgia (13%) Ipilimumab: • Pruritus (26%) • Diarrhea (23%) • Fatigue (17%) • Rash (16%)	Pembrolizumab***: • Fatigue (1%) • Diarrhea (1%) Ipilimumab: • Diarrhea (3%) • Fatigue (1%)
Robert *et al.* (2015)[11]	• Nivolumab	• Fatigue (20%) • Pruritus (17% • Nausea (17% • Diarrhea (16% • Rash (15%)	• Diarrhea (1%)
Weber *et al.* (2015)[12]	• Nivolumab	Not reported****	• Fatigue (1%) • Anaemia (1%)
Weber *et al.* (2017)[13]	• Nivolumab • Ipilimumab	Nivolumab: • Fatigue (35%) • Diarrhea (24%) • Pruritus (23%) • Rash (20%) • Nausea (15%) Ipilimumab: • Diarrhea (46%) • Pruritus (34%) • Fatigue (33%) • Rash (30%) • Nausea (20%)	Nivolumab: • Diarrhea (2%) • Rash (1%) • Elevated ALT level (1%) Ipilimumab: • Diarrhea (10%) • Elevated ALT level (6%) • Elevated AST level (4%)
Larkin *et al.* (2015)[14]	• Nivolumab • Ipilimumab • Nivolumab + Ipilimumab	Nivolumab: • Fatigue (34%) • Rash (26%) • Diarrhea (19%) • Pruritus (19% • Nausea (13%) Ipilimumab: • Pruritus (35%) • Diarrhea (33%) • Fatigue (28%) Nivolumab + pilimumab: • Diarrhea (44%) • Rash (40%) • Fatigue (35%) • Pruritus (33%) • Nausea (26%)	Nivolumab: • Diarrhea (2%) • Fatigue (1%) • Elevated ALT level (1%) Ipilimumab: • Colitis (9%) • Diarrhea (6%) • Rash (2%) Nivolumab + Ipilimumab: • Diarrhea (9%) • Elevated ALT level (8%) • Elevated AST level (6%)
Wolchok *et al.* (2017)[15]	• Nivolumab • Ipilimumab • Nivolumab + Ipilimumab	Nivolumab: • Fatigue (36%) • Rash (23%) • Diarrhea (21%) • Pruritus (21%) • Decreased appetite (12%) Ipilimumab: • Pruritus (36%) • Diarrhea (34%) • Fatigue (29%) • Rash (22%) • Nausea (16%) Nivolumab + Ipilimumab: • Diarrhea (45%) • Fatigue (38%) • Pruritus (35%) • Rash (30%)	Nivolumab: • Increased lipase level (4%) • Diarrhea (3%) • Increased amylase level (2%) Ipilimumab: • Colitis (8%) • Diarrhea (6%) Nivolumab + Ipilimumab: • Increased lipase level (11%) • Diarrhea (9%) • Increased alanine aminotransferase level (9%)
Eggermont *et al.* (2015)[16]	• Ipilimumab	• Not reported****	• Diarrhea (10%) • Colitis (7%) • Hypophysitis (5%)
Eggermont *et al.* (2016)[17]	• Ipilimumab	• Diarrhea (41%) • Rash (34%) • Increase in liver enzymes (18%) • Hypophysitis (16%) • Colitis (16%)	• Diarrhea (10%) • Colitis (7%) • Hypophysitis (4%)
Andtbacka *et al.* (2015)[18]	• T-VEC	• Fatigue (50%) • Chills (49%) • Pyrexia (43%) • Nausea (36%) • Influenza-like illness (31%)	• Cellulitis (2%) • Fatigue (2%) • Vomiting (2%)
Harrington *et al.* (2016)[19]	• T-VEC	• Fatigue (51%) • Chills (50%) • Pyrexia (40%) • Influenza-like illness (34%) • Nausea (34%)	Not reported*****

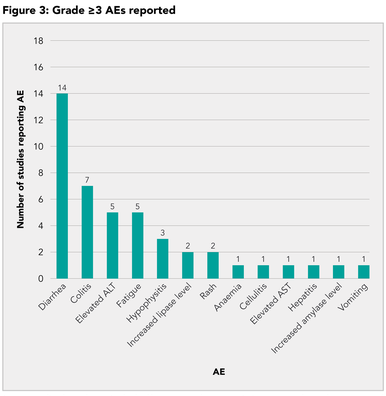
*The authors did not report any grade ≥3 AEs. **Figures reported are from 2 week group. ***Figures reported are from 3 week group. ****Authors did not report any all-grade AEs. *****Authors did not report any grade ≥3 AEs
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; T-VEC, talimogene laherparepvec

Figure 2: All-grade AEs reported



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

Figure 3: Grade ≥3 AEs reported



Note: studies have been included here more than once in instances where they reported AEs from more than one immunotherapy
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase

DISCUSSION

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

Several approaches have been taken to further understand this unmet need. For example, Kartolo *et al.* (2018)[20] 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[21] 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 immunotherapies are associated with high rates of AEs.

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

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