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REVIEW ARTICLE **OPEN ACCESS**

Immune-Related Events Effect on Melanoma

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ABSTRACT

Several studies have concluded that the introduction of CPI has been one of the most recent advancements in the fight against advanced tumors, raising survival rates by around 5 years. Studies have concluded that, it has been shown via research that the CPI was developed with the intention of improving patient survival rates. Furthermore, studies have concluded that the body gene sometimes produces an anti-tumor response that leads to the disinhibition of T cell function, which in turn leads to inflammatory side effects, or IRAE. Individuals with M who have had CPI therapy may have IRAE as a result of this. Thus, in our review, we have discussed the IR effect on melanoma in terms of adverse effects, investigations, management, and future directions.

Key words: *IR, melanoma, AE, investigations, management, future directions*

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INTRODUCTION

Furthermore, research has shown that "immune checkpoint proteins (ICP), including PD-1 and CTLA-4, stop the immune system from activating without being stopped. They do this by starting signaling pathways that limit T cell function". [1, 2] Furthermore, studies have concluded that "other ICPs include programmed death receptor-2 (PD-2) and CTLA-3. In addition, research has shown that immune checkpoint-blocking antibodies bind to immune checkpoint proteins to try to get around the way that tumors stop T cells from working".[3] Many studies have looked at "CP as a possible therapeutic target, but the main focus of current clinical use of immune checkpoint inhibitors (ICI) has been on antibodies that block CTLA-4 (ipilimumab, tremelimumab), PD-1 (pembrolizumab, nivolumab, and cemiplimab), and PDL-1 (atezolizumab, avelumab, and durvalumab)".[4] In addition to this, studies have also concluded that these "medicines have resulted in better survival and the potential for lasting responses in the treatment of melanoma, which is one of the many diseases for which they have changed the treatment". [3,4,5] Furthermore, research on advanced metastatic melanoma suggests that this treatment can be used either after surgery or to treat a disease that can't be removed. [6] According to the findings of recent studies, the treatment strategy for cancer, and particularly melanoma, has been completely transformed as a result of these new therapies.[7] While studies have also shown the "potential anti-tumor impact, which disinhibits T cell function and leads to inflammatory side effects known as immune-related adverse events (IRAE), the precise pathophysiology of it is not yet understood, and cell researchers still suggest that it arises as a result of a combination of multiple pathways involving autoreactive T cells, auto-antibodies, and numerous cytokines".[7,8] Studies have concluded that approximately half of patients treated with anti-PDI monotherapy have IRAE. Studies have concluded that to manage IRAE, steroids or, less often, immunosuppressive medications are required. [9] Moreover, studies have also concluded that "IRAE severity studies have concluded that they may involve numerous organs and mimic a wide variety of spontaneous immune-mediated diseases that are classified using common terminology criteria for adverse events (CTCAE)".[10] Addition to this, studies have also found that there is some evidence from scientific studies suggesting that patients treated with CPI have a skin adverse response characteristic of melanoma.[11] Thus, in our review we have evaluated & discussed IR effect on melanoma.

ADVERSE EVENTS [12]

1. "Skin Eruptions/ Inflammatory Eruption
2. Drug associated maculopapular Exanthem (MPE)
3. Lichenoid Reaction
4. Psoriasiform Reaction

5. Pruritus
6. Cutaneous Sarcoidosis
7. Vitiligo – like depigmentation rash (VLDR)
8. Dermatomyositis(Anti-PD1)
9. Bullous Pemphigoid (Anti-PD1, Anti-PDL-1 & Anti- CTLA-4)
10. Dermatitis Herpetiformis (Anti-CTLA-4)
11. Vasculitis (Anti-PD1)
12. Sweet Syndrome (Anti- CTLA-4)
13. DRESS (Anti-CTLA-4)
14. Grover Disease (Anti- PD1 & Anti-CTLA-4)
15. Acneiform Rash & Rosacea Alopecia (Anti-CTLA-4 & Anti-PD1 , Anti-CTLA-4 & Anti-PD1)".[12]

DERMATOLOGIC TOXICITY (DT)

Studies have concluded that "DT is the most common irAE that has been reported in patients with melanoma who are being treated with CTLA-4 or PD-1 treatment".[13,14] Studies have also concluded that "all-grade dermatologic toxicity was reported in 30–40% of patients treated with PD-1/PD-L1 inhibitors" [15,16] and in "50% of patients treated with ipilimumab, despite the fact that the majority of dermatologic irAEs were grade 1 or 2".[15,17] Furthermore, studies have also concluded that "this was the case despite the fact that the majority of dermatologic irAEs were reported. The incidence of rash of any grade was reported to be 16.7% for nivolumab and 14.3% for pembrolizumab, respectively, in a meta-analysis of dermatologic toxicity".[17] For the purpose of this study, "there were a total of eight clinical studies using nivolumab and five clinical trials involving pembrolizumab". "Vitiligo, which was only found in patients with melanoma and is connected with tumor response, has been reported in 7.5% of patients treated with nivolumab and in 8.3% of patients treated with pembrolizumab".[17,18] Studies have also concluded that "vitiligo was only observed in patients with melanoma and is related to tumor response".[18] This is a significant discovery considering that vitiligo has only been seen in patients who have melanoma.[18]

Studies have concluded that the "manifestations of the disease include maculopapular or papulopustular rash, pruritis, urticarial dermatitis, Sweet's syndrome, lichenoids, eczema, and bullous disorders".[19,20] Moreover studies have also concluded that "rash is the most common type of skin toxicity that may develop as a consequence of treatment with anti-PD-1 or anti-CTLA-4".[19,21] Studies have also concluded that "skin toxicity may also occur as a result of anti-CTLA-4 therapy".[22] Studies have also concluded that "toxicities of a severe character, including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) or drug response with eosinophilia and systemic symptoms (DRESS), are more common when an ICI combination".[22] Studies have also concluded that the emergence of symptoms typically takes place anywhere between a few days and a few weeks.[23,24] However, in other circumstances, it may not appear until after a treatment has been ongoing for a number of months.[24]

Studies have concluded that "it is feasible to treat grade 1 dermatologic irAEs by using emollients, topical corticosteroids, and/or oral antihistamines".[25,26] Researchers have also concluded that ICI may be continued even if there is toxicity in grade 2, but it must be stopped if there is no improvement in the irAE to grade 1.[25,26] Studies have also found that "ICI treatment should be stopped if there is a risk of grade 3 or 4 toxicity. Instead, systemic corticosteroids should be considered for the patient, along with other types of supportive care".[25,26] Studies have also concluded that when a patient's life is in danger, it is necessary that ICI be immediately and totally ended, and patients should be transferred to a specialist. Various other studies have concluded that when a patient's life is in danger, it is imperative that ICI be immediately and completely terminated. Thus, studies also concluded that "this is of the utmost importance in the case that there is a concern about a rare dermatologic irAE, such as SJS/TEN or Dress".[25]

GASTROINTESTINAL TOXICITY

a. Diarrhea or Colitis

Studies have concluded that "although diarrhea is often reported in patients receiving ICI therapy, the incidence is much higher in patients receiving anti-CTLA-4 blocking". According to a comprehensive review that included "10 clinical studies including patients with various types of solid tumors, there were reports of diarrhea in 27–54% of patients treated with anti-CTLA-4 therapy".[27] Additionally, studies have also concluded that "colitis was reported in 8–22% of patients who were treated with a combination of CTLA-4 and PD-1 blocking are reported to have the highest incidence of colitis, and the risk of patients suffering grade 3 or 4 symptoms is equally raised with a combination therapy as compared to monotherapy. Studies have also concluded that when using CTLA-4 monotherapy, the incidence of colitis

is lower than when using PD-1 inhibition alone".[22] Additionally, studies have also concluded that ,"colitis is exceedingly rare when using PD-1 inhibition alone. In a randomized phase III study including 945 patients with advanced melanoma, any grade of colitis was reported in 2.2% of patients treated with nivolumab, 11.3% of patients treated with ipilimumab, and 12.8% of patients treated with ipilimumab + nivolumab. 1% of patients receiving nivolumab, 7.7% of patients receiving ipilimumab, and 8.3% of patients receiving the combination of nivolumab and ipilimumab reported colitis of grade 3 or 4".[14]Studies have concluded that, "despite the fact that these diseases are often reported separately, the underlying intestinal inflammation, or colitis, is thought to be the root cause of diarrhea". Studies have also concluded that "patients who present with overt colitis may come with diarrhea, but they may also complain of fever, stomach pain, and rectal bleeding".[22] Studies have also concluded that "patients with overt colitis may also bleed from the rectal area. Patients who are suffering from overt colitis may also have an elevated risk of infection". Studies have also concluded that the average time until the initiation of GI irAEs in patients who are being treated with anti-CTLA-4 monotherapy is after the third infusion; however, symptoms may emerge as early as after the first infusion.[28] Additionally, studies have concluded that, diarrhea or colitis may recur after therapy has been discontinued, and the symptoms may present themselves in a way that is similar to those of chronic inflammatory bowel disease.[29,30]

b. Hepatitis

Studies have concluded that the "incidence of hepatitis in patients treated with ipilimumab is dose-dependent, with an incidence of 4% of any-grade hepatitis in patients treated with 3 mg/kg of ipilimumab and 15% in patients treated with 10 mg/kg of ipilimumab".[31,32] Studies have also concluded that the "incidence of hepatitis increases with increasing doses of ipilimumab. In addition to that, studies concluded that compared to 30% of patients treated with combination therapy, 1–6% of patients treated with anti-PD-1 therapy are reported to have any grade of hepatitis".[14,33] Studies have also concluded that "an elevation in AST/ALT of grade 3–4 was reported in 6–9% of patients treated with ipilimumab + nivolumab, compared with 1–2% of patients treated with either ipilimumab or nivolumab monotherapy in a phase III study of previously untreated patients with advanced melanoma".[14] Studies have also concluded that this was a "significant difference between the two treatment groups. The median time to clearing of hepatic irAEs was reported to be 3.3 weeks in a pooled safety evaluation of 576 patients with melanoma who were treated with nivolumab".[34] Another study was conducted on patients "who were given nivolumab. Hepatitis most commonly appears as an asymptomatic elevation of AST and ALT with or without elevated bilirubin"[35,20], while a more severe presentation with fulminant hepatitis has been reported.[33] Studies have also concluded that between 6 and 14 weeks after the start of treatment is the most common time for a trans aminase elevation to develop.[33]

ENDOCRINOPATHIES TOXICITY (ET)

Studies have concluded that the "ET associated with ICI include hypothyroidism or hyperthyroidism, thyroiditis, hypophysitis, primary adrenal insufficiency, and IDDM".[36] Studies have also concluded that the "most common types of endocrinopathies that have been linked to ICI are reported to be thyroid and pituitary toxicity. 0.7% and 0.2% of patients, respectively, have been reported to have had rare endocrine adverse events (irAEs) such as primary adrenal insufficiency and IDDM".[36] Studies have also concluded that "ET may present with a range of non-specific symptoms, including fatigue, headaches, or weakness, making it challenging to diagnose them".[37] Researchers also concluded that the "length of time that must pass before the onset of endocrine irAEs varies from one agent to the next". Studies have also concluded that the "median time for the onset of moderate-to-severe endocrine irAEs in patients with melanoma who are being treated with ipilimumab is 7–20 weeks".[38] Studies have also concluded that a "single-institution retrospective assessment of melanoma patients treated with ipilimumab reported a median time to onset of therapy of 4 months; however, the timing of hypophysitis onset ranged from 8 to 19 months after therapy initiation".[39] Studies have also concluded that "hypothyroidism was reported after initiation, ranging from the first five months to up to three years later".[39] Studies have also concluded that a "pooled assessment of safety events related to nivolumab reported that the median time of onset was somewhere in the vicinity of 10 weeks".[34] In contrast to other irAEs, studies have also concluded that it may be cured with treatment, endocrinopathies are typically irreversible and need long-term hormone replacement.[40]

INVESTIGATION [41]

"Complete Skin Examination
Skin Biopsy
ANA , SS-A , SS-B investiagtion should be done if autoimmune condition is suspected".

MANAGEMENT [41]

"Grade 1

1. Emollients
2. Topical Corticosteroid
3. Oral Antihistamines

Grade 2 : Hold to ICI if no improvements to grade 1

Grade 3

1. Hold to ICI
2. Treat with systemic 1-2 mg/kg/day steroid
3. Dermatology consultation"

FUTURE DIRECTION [42]

Several past studies have shown that "even though IC blockade is usually thought of as being well-tolerated, it can still cause life-threatening IRAEs, some of which may be severe and/or long-lasting. In addition, studies also concluded that ICB may be well-tolerated. In further research, it will be very important to pay particular attention to the identification of the ways in which ICB may impact the quality of life for the whole of a person's life. Also, no research has been done yet on how the possible adverse effect of steroid therapy (as a response to an IRAE) might affect how well anticancer treatment works. More biological and auxiliary pharmacogenomics studies will need to be conducted in order to answer the question of whether or not a patient's immunologic profile (such as polymorphisms or human leucocyte antigen status) makes them more likely to develop IRAEs. This will allow researchers to determine whether or not a patient's immunologic profile increases their risk of developing IRAEs".[42] In addition to the above, many past research studies have shown that "most IRAEs can be fixed with steroids, as long as the treatment starts early and at the right dose, is slowly lowered, and then stopped. Hence, according to studies, it is also essential to note that some patients may have a long-term benefit from ICB or perhaps be cured as a result of the treatment. This suggests that these patients should be closely watched for late-onset IRAEs for many years after the treatment has been started. Also, many past research studies have shown that it is important to keep an eye on and check up on patients who have survived in order to learn more about the long-term safety profile of anti-CTLA-4 and anti-PD-1 antibodies, which is still being figured out. In addition, the safety of ICB in patients who have an underlying autoimmune illness is unclear since these people have always been excluded from clinical studies. This is due to the fact that clinical trials are conducted on healthy volunteers. In light of this, it is very necessary to give careful consideration to the potential toxicity in light of the benefits that may be derived from IC ages. Thus, researchers have concluded that,It is essential for the patient and the physician to have an in-depth conversation regarding the aforementioned topics".[42]

CONCLUSION

IRAE may have an impact on patients with M who have received CPI treatment. Studies that examine the potential advantages of including dermatologists in multidisciplinary teams for the purpose of assessing IRAE in patients who are getting CPIs with the goal of enhancing their treatment outcomes are required in the future. The potential benefits of including dermatologists in these teams may be examined in these studies by age.

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