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Immune Related Events Predict the Prognosis of Melanoma(M).

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Abstract
Studies have proved that, CPI has been devised with the aim of enhancing survival rates. At times, the body generates an anti-tumor response that results in the disinhibition of T cell function which leads to inflammatory side effects or IRAE. Consequently, individuals with M who have received CPI therapy may manifest IRAE. Thus, research is warranted to explore the potential advantages of integrating dermatologists into interdisciplinary groups to assess IRAE in patients undergoing treatment with CPI in order to optimize their therapeutic results.

1. Introduction

Various studies have concluded that , Immune check point inhibitor (CPI) development has been one of the most recent advances[1] against advanced cancers by increasing survival rates approx 5 years.[2] The agents that target CPI includes cytotoxicT lymphocyte antigen-4 (CTLA-4) and programmed death receptor-1 (PD-1)[2], prevent unopposed immune activation and tissue damage by initiating signaling cascades that inhibit the T cell function.[3] Furthermore, "studies have proved that anti-CTLA-4 (e.g. ipilimumab),anti-PD1 (e.g. pembrolizumab or nivolumab) and anti-PDL1 (e.g. atezolizumab) agents are used either alone or in combination to treat advanced melanoma; renal, bladder, lung, breast, head and neck, squamous cell skin and colorectal carcinoma and haematological malignancies.[2] Additionally , according to studies in advanced metastatic melanoma ,this therapy can be gievn either adjuvantly following resection or unresectable disease.[2] Henceforth, studies conclude that, these therapies had revolutionized the treatment modality particulary for melanoma.[3] While studies have also proven the anti-tumor effect potential which disinhibit T cell function & leads to inflammatory side effects which was called as immune-related adverse events (IRAE). However,the exact pathology of it is not known yet , still reseachers suggest that it develops through combination of various pathways involving autoreactive T cell, auto-antibodies & different cytokines.[4,5] It is estimated by various studies that IRAE occur approximately 50% of patients treated with anti-PDI monotherapy. Furthermore, steroids or rarely immunosuppressive drugs are required to control IRAE.[1] Furthermore, according to IRAE severity studies have concluded that , they can involve multiple organs & resemble wide variety of spontaneous immune-mediated disease which are graded using common terminology criteria for adverse events (CTCAE).[6] Some studies have shown evidence to suggest that, melanoma specific skin adverse reaction is seen in CPI treated patients.[7]

2. Literature Review

1. **Voskens et al.,(2013)[8]** conducted a research on total of 752 patients, all of whom had melanoma

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treated with anti-CTLA4 therapy. They concluded that cutaneous reactions were common, but severe reactions in grades 3 or 4 were rare.

2. **Hofmann et al.,(2016)[9]** conducted their study on a total of 496 patients who were given treatment for melanoma with anti-PD1 agents. They concluded that a total of 43 patients showed symptoms of skin rashes out of 496.
3. **Bottlaender et al.,(2020)[10]** conducted a study on a total of 189 patients with melanoma treated with anti-PD1 therapy alone and identifieda frequency of cutaneous IrAE of 49%, with 92 patients intheir observational cohort study experiencing skin toxicity ofany grade. Of these, 18 showed 'skin eruption', 16 showed vitiligo, and five showed isolated pruritis.Grade 3–4 skin toxicity was diagnosed in five patients (2.6%). Atopy, hypereosinophilia, thyroiditis, and renal toxicity showed significant associations with cutaneous AE. Patients with skin eruptions, vitiligo, or any type of cutaneous AE had a better overall survival. They concluded that cutaneous AEs are frequent and often manageable toxicity and were a predictor of tumor response in melanoma patients under anti-PD-1 therapy.

IRAE

a. Skin Eruptions/ inflammatory eruption

The term was initially introduced by Coleman and colleagues to encompass lichenoid, eczematous, psoriasiform, and maculopapular drug exanthems that result in recurrent reactions in patients undergoing treatment with checkpoint inhibitors.[11]

b. Drug-associated maculopapular exanthem (MPE)

A study was conducted wherein total of nine patients were present, who underwent treatment with anti-CTLA-4 suggests that, the observed reaction was similar to conventional antibiotic drug eruptions.[12] Furthermore, studies conducted by Bottlaender et al.,[10] and Hofmann et al.,[9] have categorized the clinical presentations of MPE as a 'skin eruption' or 'rash'. Additionally, persistent observation in drug-related malignant pleural effusion (MPE) is that the trunk is predominantly impacted, while the face, palms, and soles remain unaffected.[13] There exists a possibility that a certain percentage of the maculopapular and morbilliform rashes diagnosed in clinical settings may correspond to some of the rashes that have been confirmed through biopsy.[2]

c. Lichenoid Reaction(LR)

Studies have concluded that, manifestation of LR in melanoma treated with CPI may appear as papules or plaques that are either violaceous or erythematous in color and are often accompanied by pruritus. Studies have shown evidences for presence of LR on palms, soles, mucosal surfaces and nails.[14,15] But at times , studies have also shown only mucosal lesions.[2] According to various past studies ,microscopic examination showed, a dense infiltration of lymphocytes in a band-like pattern along with dermo-epidermal junction. This infiltration may be mixed with both CD4 and CD8-positive cells or may be predominantly composed of CD4-positive cells. Additionally, hyperkeratosis and hypergranulosis are present.[16] Furthermore, studies conclude that, if there is a presence of parakeratosis then it is indicative of atypical histological characteristics.[2]

d. Eczematous Reaction (ER)

Various past studies have shown that, ER can manifest as conventional pruritic, indistinct areas/patch, or plaques of discoid eczema.[2] Studies conclude its distribution pattern as over torso and extremities; however, it is possible for the face, scalp, axillae, and genital regions to be affected.[2] Hwang and colleagues, conducteda study which includes patients with metastatic melanoma (MMM) who received anti-PD1 treatment . They found that , there was an formation of eczema after a duration of 10 months, with a higher likelihood of occurrence observed in those who underwent longer treatment.[17]

e. Psoriasiform Reactions (PR)

According to various past studies, PR was considered as to manifest as either a de novo occurrence or as a flare-up for preexisting psoriasis.[10,18] Studies have also concluded that, the mean duration for the manifestation of psoriasis in patients treated with anti-PD1 is approximately 50 days, with a tendency for those with pre-existing psoriasis to experience exacerbation prior to this period. The most prevalent manifestation of psoriasis is the occurrence of pink-red papules with silvery scales at localized extensor sites.[11,18] However,

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it is noteworthy that inverse-pattern psoriasis or palmoplantar pustulosis are infrequently observed.[2]

f. Pruritus

According to many past studies, it is frequently cited as a prevalent cutaneous IRAE.[19] Studies concluded that, this phenomenon is typically correlated with one of the aforementioned inflammatory outbreaks, although it may occur infrequently in a solitary manner. Furthermore, studies have also concluded that, it can significantly impact the quality of life among individuals undergoing CPI therapy for MMM, with a reported incidence of 14–21% for those receiving anti-PD1 treatment and 25–36% for those receiving anti-CTLA4 treatment. In addition, studies proved that, sensation of itch is commonly observed among individuals who undergo combination therapy, with a reported incidence ranging from 33% to 47%.[19,20]

g. Cutaneous sarcoidosis (CS)

According to research studies, CS is also known as sarcoid-like granulomatous reactions (S-GR). It has been concluded that it manifest as erythematous papular or nodular lesions that are embedded subcutaneously. These lesions are typically distributed on the arms and intertriginous areas.[21] According to studies, prevalence of this phenomenon appears to be higher among patients with melanoma who have received anti-CTLA4 treatment as compared to those who have undergone treatment for other types of cancer. Hence,this observation may serve as a potential response indicator for certain patients with MMM.[22] Studies have also proven that , observed lesions have the potential to manifest as either annular formations or plaques.[14] There have been reports of other organs being impacted by sarcoidosis, and instances of cutaneous sarcoidosis occurring concurrently with bilateral anterior uveitis and elevated serum angiotensin-converting enzyme levels have been documented.[13] Patients may exhibit pulmonary manifestations, such as mediastinal lymphadenopathy or inflammatory lung disease, which can pose a clinical challenge in distinguishing them from the progression of MMM according to studies.[14]

h. Vitiligo-Like Depigmenting Rash(VLDR)

Studies concluded that , this type of rash is observed to manifest in several months after the initiation of CPI therapy and, in some cases, subsequently on conclusion of the treatment.[2] Studies showed that, incidence of VLDR is notable in individuals with melanoma, with an estimated occurrence of approximately 10% among patients receiving anti-PD1 agents.[9] Nevertheless, it is said to be less frequent in other forms of tumors, such as pulmonary carcinoma by various researches. Studies also conclude that , the distribution of an anatomical feature is commonly observed to encompass the facial region, neck, upper torso, and upper extremities. Focal patches have been observed to impact scars or the locations of cutaneous metastases. Although lesions typically do not exhibit symptoms, they may be preceded by pruritis or a non-specific maculopapular rash.[13] Studies showed the correlation between VLDR and enhanced tumor response to CPIs as stastically significant.[22] Various past studies have shown that, the histological aspect in this condition comprise of lack of epidermal melanocytes at the dermo-epidermal interface & presence of CD8 T-cell infiltrate that exhibits an overexpression of CXCR3, along with elevated levels of interferon-c and tumor necrosis factor.[13] Additionaly , researches conclude that ,VLDR arises due to a cross-reactivity phenomenon that occurs between healthy melanocytes and melanoma tumors, which involves shared antigens such as MART-1, GP100, tyrosinase-related proteins 1 and 2, or tyrosinase.[14]

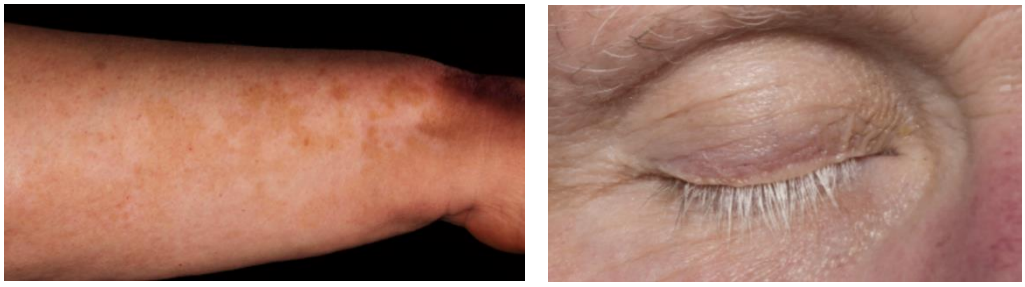

Figure 1: VLDR WITH MELANOMA TREATED WITH CPI.[2]

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OTHER EVENTS

1. Dermatomyositis (Anti-PD1)
2. Bullous Pemphigoid (Anti-PD1 , Anti-PDL-1 & Anti-CTLA-4).
3. Dermatitis Herpetiformis (Anti-CTLA-4)
4. Vasculitis (Anti-PD1)
5. Sweet Syndrome (Anti- CTLA-4)
6. DRESS(Anti-CTLA -4)
7. Grover Disease (Anti-PD1 & Anti-CTLA-4)
8. Acneiform Rash & Rosacea Alopecia (Anti-CTLA -4 & Anti-PD1 , Anti-CTLA-4 & Anti-PD1).

3. Conclusion

M patients who have undergone CPI treatment may exhibit IRAE. Future studies may investigate the potential benefits of incorporating dermatologists into multidisciplinary teams for the evaluation IRAE in patients receiving CPIs, with the aim of enhancing their treatment outcomes are needed.

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