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Efficacy and Toxicity of Pembrolizumab in Pediatric Metastatic Recurrent Melanoma

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Abstract. *Background/Aim: Malignant melanoma is a rare disease in the pediatric population and there are no recommendations regarding its management in children, while the current standard of care in metastatic or unresectable melanoma in adult patients includes immunotherapy (anti-CTLA-4 and anti-PD-1 antibodies). Advances in the management of adults with melanoma offer the prospect of promising therapeutic options for children. Case Report: We describe a case of a 7-year-old patient with recurrent metastatic melanoma, for whom pembrolizumab was used as an adjuvant therapy on compassionate use basis. Conclusion: Due to adverse events, the treatment was discontinued after 5 months of pembrolizumab, but with 12-months of follow-up, patient remains in complete remission.*

Malignant melanoma is a very rare disease in children. Less than 1% of all melanoma cases occur in prepubertal patients. Conflicting data exist on the outcomes of pediatric melanoma compared to older patients. More recent analyses suggest a better outcome in children when compared with adults, what implies that children might have a different biologic form of malignant melanoma than adults (1).

Nowadays the standard of care in metastatic or unresectable melanoma in adult patients include immunotherapy with anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) antibodies, which is an unprecedented breakthrough in the treatment of this malignancy and has contributed to significantly improved prognosis. However, an access to modern therapeutic options in children is currently limited. Recently, the only new immune medication registered for the use in children aged over 12 years is ipilimumab, an anti-CTLA-4 antibody. Other immunotherapeutics, such as anti-PD-1 inhibitors pembrolizumab and nivolumab or targeted therapies, are registered only for adult patients (2, 3).

With the rarity of melanoma in children and the lack of clinical trials, there are no recommendations on management in this malignancy in pediatric patients. In exceptional cases, the ultimate therapy can be the use of off-label drugs. In this report we present a case of a child with metastatic recurrent melanoma, for whom pembrolizumab was successfully applied as a method of treatment.

Case Report

A 4-year-old female patient was diagnosed for malignant melanoma stage IIIC by TNM classification, while carrying no *BRAF* mutation, with primary tumor localized on right arm and presence of metastases to axillary lymph nodes. Total surgical resection with wide margin of the primary tumor and removal of the axillary node package was performed followed by adjuvant therapy with interferon α-2B (IFN α-2B). The patient received IFN α-2B over one year in two phases: induction (20 million Units/m^2 *i.v.*, 5 days/week for 4 weeks) and maintenance (10 million Units/m^2 *s.c.* 3 times/week for 48 weeks). No adverse events (AEs) were observed during treatment with IFN α-2B. After the end of the treatment, complete response (CR) persisted for two years.

Two months after the end of the IFN α-2B therapy, autoimmune choroidal inflammation of the right eye was diagnosed in the patient. Topical steroids were sufficient to keep the diseases stable without exacerbation.

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At the age of 7 years, the patient was diagnosed for recurrent melanoma with two foci localized in the soft tissue of the right forearm and right thigh (Figure 1). Both changes were surgically removed, histologically confirmed (*BRAF*-negative) and re-treatment with IFN α-2B was applied.

Two months later, PET scan was performed, and the presence of new lesions suspected of metastases within the soft tissues of the right thigh were revealed. Metastases were surgically resected, followed by adjuvant therapy with pembrolizumab, which was implemented on compassionate use basis. The drug was applied intravenously at dose of 2 mg/kg every 3 weeks. Based on PET imaging after the third dose of the drug, CR was achieved.

After the fourth dose of pembrolizumab, a decreased vision on the right eye with exacerbation of uveitis and pain in the left knee and left foot were observed. Thus, systemic oligoarticular type of juvenile idiopathic arthritis (JIA) was diagnosed. With the administration of steroids and temporary discontinuation of pembrolizumab, remission of the articular symptoms and stabilization of uveitis was achieved.

After four weeks break, the patient received three next courses of pembrolizumab simultaneously with low-dose steroids. However, recurrence of arthritis and significant exacerbation of uveitis has developed, which this time was not controlled by increasing doses of steroids. Due to development of Cushing syndrome, significant deterioration of the quality of life and the risk of blindness in the right eye, a decision about cessation of the treatment with pembrolizumab was made. Patient received seven doses of pembrolizumab in total, with CR of melanoma symptoms confirmed by PET scan. Currently, with 12-months of follow-up after discontinuation of the therapy, a CR is observed both clinically and in MRI imaging. Symptoms of JIA have been managed with steroids and methotrexate for 4 months after the end of the immunotherapy with complete resolution.

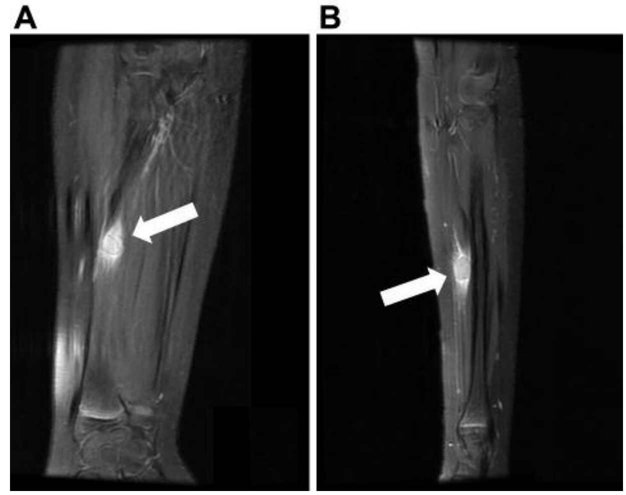

Figure 1. *Melanoma metastases in the soft tissues of the (A) thigh and (B) forearm, visualized in the MRI.*

Discussion

According to NCCN Guidelines for malignant melanoma in adult patients, the adjuvant immunotherapy should be considered in all cases with distant metastatic disease after primary treatment (4). The use of adjuvant high-dose interferon in adult and pediatric patients with high-risk melanoma is controversial. Those who dispute the use of adjuvant interferon cite modest benefit at the expense of cost and toxicity as arguments against its use (5). Currently, there are three immunomodulating agents available for melanoma, which were shown to improve overall survival in patients with metastatic melanoma without *BRAF* mutation: pembrolizumab, nivolumab and ipilimumab (2, 6).

There exist no data in the literature on the use of anti-PD-1 or anti-CTLA-4 in pediatric melanoma. In our patient, after the second progression, and dismal effect of IFN, pembrolizumab was applied on compassionate use basis. However, due to immune-related adverse events, the treatment was discontinued after 5 months of therapy. Nevertheless, with 12-months of follow-up, the child is free from progression. The immunotherapy was stopped because of adverse events occurring after 7th dose of pembrolizumab. Withdrawal of immunotherapy and careful management of JIA were necessary for the alleviation of symptoms resulting of adverse events.

Pembrolizumab is an anti-PD1 monoclonal antibody, approved for treatment of metastatic melanoma in adults. Pembrolizumab mediates its antitumour effect by unleashing latent tumor-specific T-cell responses. Chronic PD-1 blockade may be marked by immune dysregulation, which can manifest in a diverse range of organ-related toxicities. The incidence of these immune-related adverse events (irAEs) tends to increase slowly with continued exposure to anti-PD1 therapy. Most irAEs related to PD1 blockade appear during the first 6 months of treatment (7, 8). In one study, the incidence of AEs involving the use of pembrolizumab was 12%. These patients experienced grade III-V° of drug-related AEs. The most common AEs were pneumonitis, rash, pruritus, endocrinopathies, hepatitis, gastrointestinal diarrhea and colitis. Fatigue was often experienced among patients receiving therapy with pembrolizumab. The arthritis and uveitis (any grades) are described in 5.2% and <1% patients, respectively, after treatment with pembrolizumab (9-12). Most irAEs occur during the first 2 to 6 months of treatment, however, these can be effectively managed with the use of corticosteroid treatments (13).

Robert *et al.* described long-term follow-up in patients with metastatic melanoma treated with pembrolizumab, where 19 patients discontinued treatment before second course of immunotherapy because of AEs or per investigator decision. Among these patients 78.9% remained in CR at data cutoff (14). Therefore, discontinuation of the therapy after 7th cycle of pembrolizumab in our patient, will not be equivalent to the lack of effectiveness of the treatment.

In conclusion, the 5-months use of pembrolizumab in a child with advanced melanoma was effective. The child stays in CR after two previous relapses of disseminated melanoma. The side-effects observed after drug administration were manageable.

Conflicts of Interest

None of the Authors have any conflicts of interest to disclose.

Authors' Contributions

Design of the study: AM, MW, JS. Collection and analysis of data: AM, PG, MM. Writing draft: AM. Critical revision: JS. Final approval of the manuscript: all authors.

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