Dermatology Practical & Conceptual

Pembrolizumab Versus High-Dose Interferon-α2b as Adjuvant Therapy for Pediatric Melanoma: A Retrospective Study

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ABSTRACT

Introduction: Pembrolizumab is well-tolerated in pediatric patients with advanced tumors, consistent with results in adults. However, information on the safety and efficacy of adjuvant pembrolizumab in children and adolescents with melanoma is lacking.

Objectives: To compare pembrolizumab versus high-dose interferon-α2b (HDI) as adjuvant therapy in pediatric patients with melanoma.

Methods: We performed a retrospective study of pediatric patients diagnosed with melanoma between January 2008 and April 2022. Relapse-free survival (RFS) and the 1-year RFS rate were compared between patients receiving adjuvant pembrolizumab or HDI.

Results: Seventy-five pediatric patients with melanoma were screened from a database of 6,013 patients. Twenty-four patients were finally enrolled, of whom 9 received pembrolizumab and 15 received HDI as adjuvant therapy. By August 31, 2022, the median follow-up times were 23.6 months and 98.7 months in the pembrolizumab and HDI groups, respectively. There was no significant difference in median RFS between two groups (not reached versus 38.7 months, P = 0.11). The median overall survival was not reached in either group. The 1-year RFS rates were 88.9% and 66.7% in the pembrolizumab and HDI groups, respectively. All adverse events in the pembrolizumab group were grade 1 or 2, but grade 3–5 adverse events occurred in two (13%) patients receiving HDI.

Conclusions: RFS was similar in pediatric patients with melanoma receiving adjuvant pembrolizumab or HDI, but pembrolizumab was associated with a reduced risk of recurrence and a more favorable safety profile. However, due to the small sample size and differences in follow-up time, larger and prospective studies are still warranted to explore better adjuvant therapies for pediatric melanoma.

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Introduction

Melanoma is a rare disease in the pediatric population compared with its incidence in adults, with an incidence of 0.7–0.8 per million per year in the first decade of life, rising to >10 per million per year in adolescents aged 15–19 years [1]. There are three subtypes of pediatric melanoma: spitzoid melanoma, melanoma arising in a congenital melanocytic nevus, and conventional (also known as adult-type) melanoma [2]. Spitzoid melanoma is one of the most common subtypes of pediatric melanoma, showing distinct histopathological and genetic patterns compared with adult melanoma, including a greater Breslow thickness at diagnosis [3]. Most published data on pediatric melanoma have involved retrospective, single-institution studies with small samples or case reports, and few prospective studies have been conducted. Although various therapies, including ipilimumab, pembrolizumab, nivolumab, and combination BRAF-MEK inhibitors, make a huge difference in the treatment of melanoma in adults, scanty information on the use of these therapies in pediatric melanoma is available.

Pembrolizumab is a highly selective, humanized, IgG4 monoclonal antibody with a favorable safety profile and good efficacy and durability, which has been approved by the US Food and Drug Administration (FDA) for the treatment of several tumor types, including melanoma, in both adults and children. An interim analysis of the KEYNOTE-051 study reported on the use of pembrolizumab in children with advanced cancer, including eight cases of pediatric melanoma. Pembrolizumab showed favorable tolerance and encouraging antitumor activity in pediatric patients with relapsed or refractory Hodgkin lymphoma, but had low antitumor activity in most pediatric tumor types [4]. Inhibitors of programmed cell death-1 (PD-1) have not been explored as adjuvant therapies for pediatric melanoma.

Previous clinical trials demonstrated that adjuvant high-dose interferon (IFN)-α2b (HDI) had similar safety profiles in pediatric and adult melanoma patients [5]. In this study, we retrospectively analyzed and compared the outcomes of pediatric patients with completely resected melanoma treated with adjuvant pembrolizumab or HDI.

Methods

Study Design and Patients

This was a multicenter, retrospective study of pembrolizumab versus HDI as adjuvant therapy in pediatric patients with melanoma treated at three tertiary hospitals in China. The eligibility criteria (Figure 1) were: 1) <18-years-old; 2) diagnosis of completely resected stage IIB/IIC/III/IV melanoma; 3) diagnosis from January 1, 2008 to April 30, 2022; 4) pembrolizumab adjuvant therapy (2 mg/kg up to a maximum of 200 mg every 3 weeks via intravenous infusion) or HDI adjuvant therapy (18×10^6 IU/m^2 per day IFN-α2b subcutaneously on days 1–5 for 4 weeks, followed by 9×10^6 IU/m^2 per day IFN-α2b three times a week subcutaneously) within 3 months after surgery. Clinical data were extracted from medical records, including age, sex, primary site, histologic subtype, Breslow tumor thickness, ulceration, date of surgery, date of recurrence, date of death, and side effects graded according to the National Cancer Institute common toxicity criteria version 4.03. Relapse-free survival (RFS) was defined as the time from the start of adjuvant treatment to the date of first recurrence (local, regional, or distant metastasis) or death from any cause. The 1-year RFS rate, overall survival (OS), and safety were also assessed. Informed written consent was obtained from all patients. This study was approved by the Institutional Review Board of Peking University Cancer Hospital and was conducted according to Declaration of Helsinki Principles.

Statistical Analysis

All statistical analyses were performed using R version 4.2.1. Survival curves were plotted using the Kaplan-Meier method

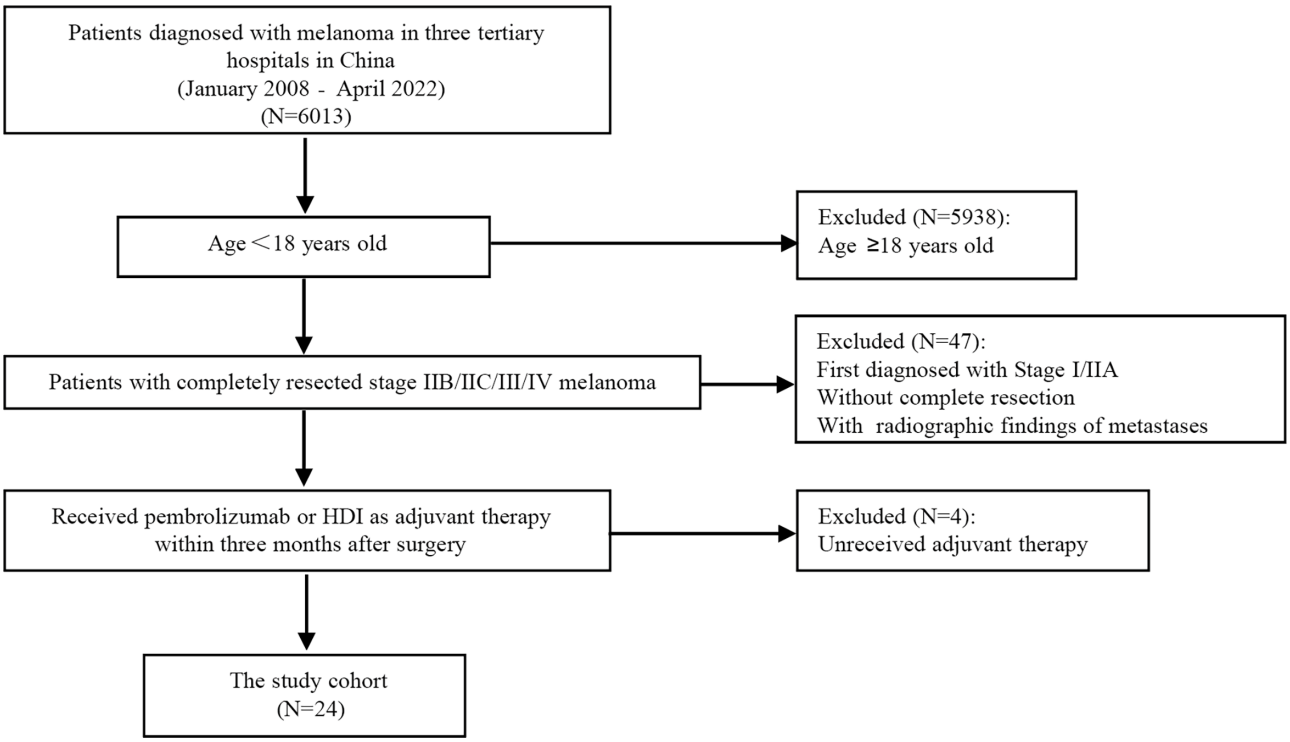

Figure 1. Flowchart of inclusion and exclusion criteria for this study.

Table 1. Clinical characteristics of pediatric patients treated with pembrolizumab as adjuvant therapy.

ID	Age	Sex	Location	Stage	Mutation	ECOG
P1	6	M	right heel	T4bN0M0/IIC	unknown	0
P2	14	F	vulvar mucosa	T4bN0M0/IIC	wild	1
P3	13	F	vulvar skin	T3bN1bM0/IIIC	NRAS Q61R	0
P4	15	M	right thigh	T4aN3bM0/IIIC	wild	0
P5	15	F	right buttock	T4bN0M0/IIC	wild	1
P6	11	F	left forearm	T4bN0M0/IIC	wild	0
P7	7	F	face	T2aN1bM0/IIIB	wild	0
P8	14	F	right calf	T3bN1cM0/IIIC	BRAF V600E	0
P9	7	F	left upper arm	T4bN0M0/IIC	wild	0

ECOG = Eastern Cooperative Oncology Group performance status score.

and compared between groups using log-rank tests. Categorical data were analyzed using χ^2 or Fisher's exact tests.

Results

Patient Characteristics

Seventy-five pediatric patients with melanoma were screened from a database of 6013 patients at three hospitals between January 1, 2008 and April 30, 2022. Twenty-eight patients had completely resected stage IIB/IIC/III/IV melanoma, of whom 24 patients were treated with pembrolizumab (N = 9; Table 1) or HDI (N = 15; Table 2) as adjuvant therapy. There were 12 (50%) male and 12 (50%) female patients, and the median age was 13.5 years (interquartile range 9.5–14.5). Twenty-two (92%) patients had stage II/III melanoma and only two (8%) patients had stage IV melanoma. There were 18 cases of cutaneous, three acral, one mucosal, and two primary unknown melanomas. Most patients had a BRAF/RAS/NF1 triple wild-type genotype, while one patient had a BRAF V600E mutation and two patients had NRAS Q61R mutations. There was no significant difference in baseline characteristics between the two groups (Table 3).

Table 2. Clinical characteristics of pediatric patients treated with high-dose interferon-α2b as adjuvant therapy.

ID	Age	Sex	Location	Stage	Mutation	ECOG
H1	13	M	left upper arm	T4bN0M0/IIC	unknown	0
H2	15	M	left upper arm	TxN1bM0/III	wild	0
H3	14	F	left middle finger	T4bN2bM0/IIIC	wild	1
H4	14	M	right groin	TxN3bM0/III	unknown	1
H5	13	M	not known	TxNxM0/III	wild	1
H6	12	M	scalp	T4aN0M0/IIB	wild	0
H7	16	M	left upper arm	T4bN0M0/IIC	unknown	0
H8	15	M	not known	TxNxM1c/IV	unknown	1
H9	8	M	right knee	TxN0M1a/IV	wild	1
H10	17	F	vulvar skin	T4bN0M0/IIC	*NRAS* Q61R	0
H11	8	F	dorsum of right foot	TxN3aM0/III	wild	0
H12	14	M	right shoulder	T3aN1aM0/IIIB	unknown	0
H13	11	F	left heel	T3bN0M0/IIB	unknown	0
H14	8	F	scalp	T4aN2cM0/IIIC	unknown	0
H15	14	M	scalp	T4aN0M0/IIB	wild	0

ECOG = Eastern Cooperative Oncology Group performance status score.

Efficacy

By the cut-off date of August 31, 2022, the median follow-up times were 23.6 months (95% CI: 8.9–not reached [NR]) for the pembrolizumab group and 98.7 months (95% CI: 63.9–NR) for the HDI group. Six (6/9, 67%) patients in the pembrolizumab group and 10 (10/15, 67%) patients in the HDI group completed 1 year of treatment. Eleven (46%) patients had disease recurrence, including one (1/9, 11%) in the pembrolizumab group and 10 (10/15, 67%) in the HDI group. The patient in the pembrolizumab group who relapsed had a NRAS Q61R mutation. One (1/9, 11%) patient in the pembrolizumab group and five patients (5/15, 33%) in the HDI group relapsed with distant metastases. No patients in the pembrolizumab group and six (6/15, 40%) patients in the HDI group died. The median RFS was not reached in the pembrolizumab group and the median RFS in the HDI group was 38.7 months (95% CI: 10.8–NR; hazard ratio 0.23; 95% CI: 0.06–0.82; P = 0.11) (Figure 2). The median OS was not reached in either group. The 1-year RFS rates were 88.9% (95% CI: 70.6–100) and 66.7% (95% CI: 46.6–95.3) and the 2-year RFS rates were 88.9% (95% CI: 70.6–100) and 60.0% (95% CI: 39.7–90.7) in the pembrolizumab and HDI groups, respectively.

Safety

Five (33%) patients in the HDI group discontinued treatment due to disease recurrence but no patient discontinued treatment due to adverse events. One patient in the pembrolizumab group discontinued treatment due to disease recurrence and one patient discontinued treatment due to an adverse event. One patient treated with pembrolizumab was still receiving treatment by August 31, 2022. Adverse events with any cause occurred in 79% (19/24) of patients overall, 44% (4/9) of patients in the pembrolizumab group, and 100% of patients in the HDI group (15/15) (P = 0.003). The adverse events are summarized in Table 4. Most adverse events were grade 1 or 2, and grade 3 treatment-related adverse events (TRAEs), including neutropenia, alanine aminotransferase (ALT) elevation, and aspartate aminotransferase (AST) elevation, only occurred in two patients in the HDI group. The most common adverse events in the HDI group were myelosuppression, pyrexia, and nausea. Adverse events did not lead to any deaths in either group. There were fewer adverse events in the pembrolizumab group compared with the HDI group, including hyperthyroidism (N = 2, grade 1), rash (N = 2, grade 1), ALT elevation (N = 1, grade 1), AST elevation (N = 1, grade 1), leucopenia (N = 1, grade 1), neutropenia (N = 1, grade 1), and alopecia (N = 1, grade 2).

Conclusions

Pediatric melanoma is a rare type of tumor in the pediatric population, qualifying as an "orphan" disease according to the definition adopted by pediatric cooperative groups for rare childhood tumors in Europe [6]. Given its rarity,

Table 3. Baseline characteristics of patients.

	Pembrolizumab (n=9)	HDI (n=15)	P
Age			
Mean (SD)	11.3(3.7)	12.8(2.9)	0.290
≤ 10	3(33)	3(20)	0.635
> 10	6(67)	12(80)	
Sex			0.089
Male	2(22)	10(67)	
Female	7(78)	5(33)	
Subtype			0.583
Cutaneous	7(78)	11(73)	
Acral	1(11)	2(13)	
Mucosal	1(11)	0	
Primary unknown	0	2(13)	
Stage			0.833
II	5(56)	6(40)	
III	4(44)	7(47)	
IV	0	2(13)	
Mutation status			0.170
BRAF	1(11)	0(0)	
RAS	1(11)	1(7)	
*NF*1	0(0.0)	0(0)	
*BRAF/RAS/NF*1 triple wild type	6(67)	7(47)	
Unknown	1(11)	7(47)	
ECOG PS			0.669
0	7(78)	10(67)	
1	2(22)	5(33)	

ECOG PS = Eastern Cooperative Oncology Group performance status score.
HDI = high-dose interferon-α2b; SD = standard deviation.

epidemiological and natural history studies of pediatric melanoma are not well-understood. Distinct from melanoma in adults, spitzoid melanoma is one of the most common histologic subtypes in pediatric patients with melanoma. Interestingly, a recent meta-analysis including 1002 patients with melanoma have demonstrated that spitzoid melanoma with higher occurrence in children younger than 10 years harbors higher Breslow thickness and more propensity to nodal metastasis than non-spitzoid melanomas, but shows a more indolent biological behavior and a better prognosis [7]. Additionally, nevus-associated melanoma is more frequently observed in children than in adults, as a higher number of pediatric melanomas are associated with congenital nevi in younger patients. All these results suggest a different biological behavior of pediatric melanoma from the adult melanoma. Compared with melanoma in adults, there is limited evidence to support the use of different therapies for melanomas in children and adolescents. Current management guidelines for pediatric melanoma are mainly based on experience of therapies in adults, and the efficacy and safety of these therapies in pediatric patients remains unclear. Considering the differences between pediatric and adult melanoma, there is thus a need to identify effective systemic adjuvant therapies to reduce the risk of recurrence and improve survival in pediatric patients with melanoma.

Adjuvant therapy with PD-1 inhibitors reduced the risk of recurrence or death by 40%–50% and significantly increased RFS in patients with resected stage III/IV melanoma [8-10]. Adjuvant immunotherapy is currently a standard treatment for stage III/IV cutaneous melanoma, but there is no standard adjuvant therapy for stage IIB and IIC melanomas. In the phase 3 KEYNOTE-716 study, adjuvant

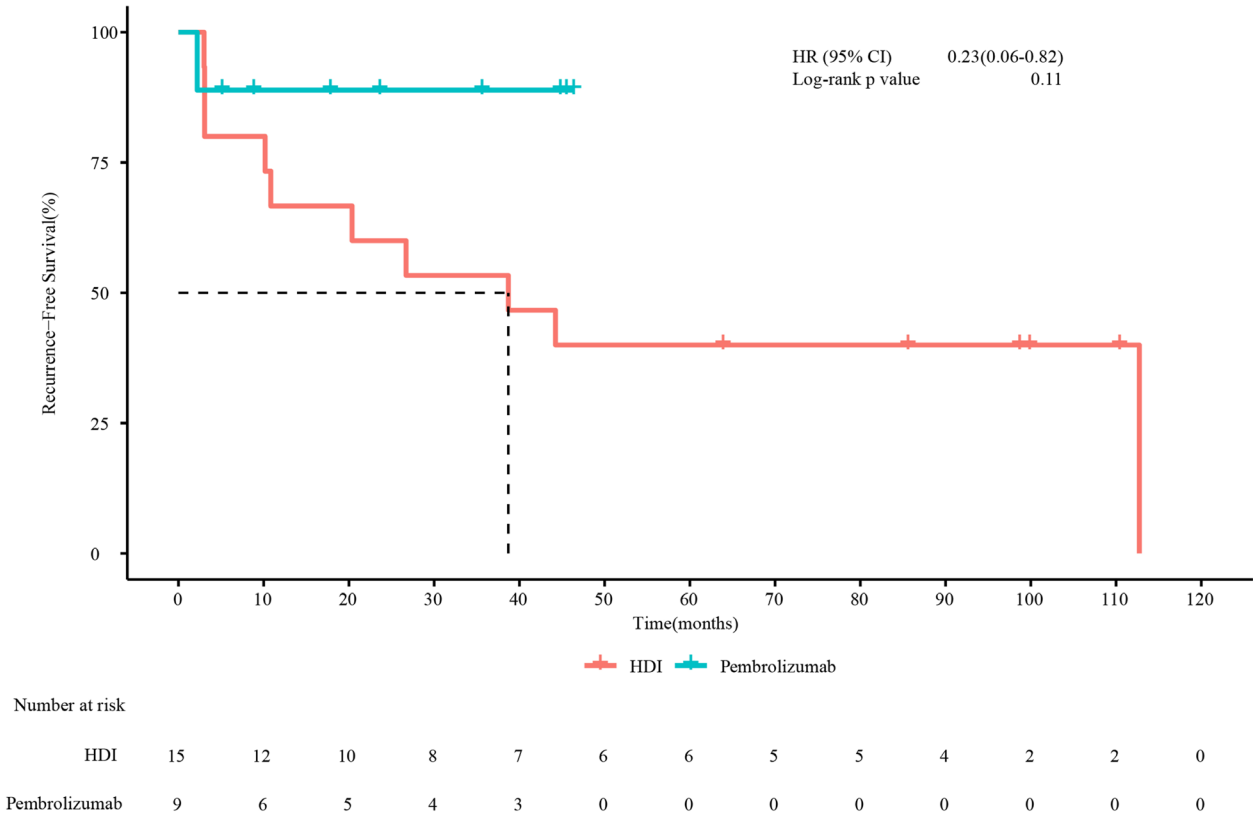

Figure 2. Kaplan-Meier estimates of recurrence-free survival in pediatric patients with melanoma treated with pembrolizumab or high-dose interferon-α2b.

CI = confidence interval; HR = hazard ratio.

Table 4. Adverse events in pediatric patients with melanoma treated with pembrolizumab or high-dose interferon-α2b.

Adverse event, N (%)	Pembrolizumab (N = 9)		HDI (N = 15)	
	Any	Grade ≥3	Any	Grade ≥3
Any cause adverse event	4(44)	0	15(100)	2(13)
Treatment-related adverse event	4(44)	0	15(100)	2(13)
Leucopenia	1(11)	0	14(93)	0
Neutropenia	1(11)	0	13(87)	1(7)
Pyrexia	0	0	13(87)	0
Nausea	0	0	7(47)	0
Hyperthyroidism	2(22)	0	0	0
ALT elevation	1(11)	0	3(20)	1(7)
AST elevation	1(11)	0	3(20)	1(7)
Rash	2(22)	0	2(13)	0
Fatigue	0	0	4(27)	0
Myalgia	0	0	2(13)	0
Alopecia	1(11)	0	0	0
Thrombocytopenia	0	0	1(7)	0
Wenckebach block	0	0	1(7)	0

pembrolizumab significantly reduced the risk of recurrence or death in patients with resected stage IIB or IIC melanoma, compared with placebo, with 12-month RFS rates of 90% and 83% and 18-month RFS rates of 86% and 77% in the pembrolizumab and placebo groups, respectively [11]. In addition, each group included one pediatric patient, and on the basis of these data, the FDA approved pembrolizumab as adjuvant therapy for adult and pediatric patients with high-risk

stage II and stage III melanomas. However, information on the use of immunotherapy as adjuvant therapy for pediatric patients is limited. Most studies have investigated immunotherapy in pediatric patients with advanced tumors. To date, nivolumab (NCT0230445848 [12]), pembrolizumab (NCT0233266849 [4]), atezolizumab (NCT0254160450 [13]), and avelumab (NCT0345182551 [14]) have been investigated as monotherapies for recurrent and refractory pediatric tumors, but only 3% of patients with solid tumors experienced an objective response across all four trials. Compared with adult cancers, most pediatric cancers have lower mutational burdens and fewer infiltrating T cells, which may account for this lack of efficacy [15]. The KEYNOTE-051 study found no objective responses in the eight enrolled pediatric patients with cutaneous melanoma who received pembrolizumab treatment [4]. The combination of PD-1 and cytotoxic T lymphocyte-associated antigen-4 blockade have added benefit compared with monotherapy in adult patients; however, the combination of ipilimumab/nivolumab does not seem to exert synergistic effects in pediatric patients. In ADVL1412, only two pediatric patients achieved partial responses among 55 evaluable patients receiving combination ipilimumab/nivolumab [16]. Overall, in contrast to the impressive responses seen with adult cancers, most pediatric cancers seem to have a poor response to immunotherapies. Whether the efficacy and safety profile of adjuvant pembrolizumab treatment are the same in pediatric patients as in adult patients remains unclear. A case report described a 7-year-old patient with recurrent metastatic melanoma who underwent complete resection of metastases and received adjuvant pembrolizumab. Although pembrolizumab treatment only lasted for 5 months because of adverse events (arthritis and uveitis), the patient had no relapse within 1 year of follow-up [17]. Only one patient in the pembrolizumab group in the current study had a recurrence and the 1-year RFS rate was 88.9%. In addition, the median RFS was not reached in pembrolizumab group. Thus, although there was no significant difference between the pembrolizumab and HDI groups, pembrolizumab seemed to be associated with a lower risk of recurrence.

The safety of adjuvant immunotherapies in pediatric patients with cancer is unclear. Although immune checkpoint inhibitors have similar adverse effects in children and adults, the most common adverse events in pediatric patients, unlike adult patients, were fatigue and fever. Elevated transaminase was the most common immune-related adverse event, while immune-related adverse events such as elevated lipase, thyroiditis, pleural and pericardial effusions, and colitis were less common in pediatric than in adult patients. In KEYNOTE-051, pembrolizumab was well tolerated in pediatric patients, with adverse events of any grade, mostly grade 1 and 2, occurring in 149 (97%) patients. The most frequent grade 3–5 TRAEs were decreased lymphocyte count and anemia. Two patients had grade 5 toxicities including treatment-related pneumonitis, pleural effusion, and pulmonary edema [4]. In the current study, pembrolizumab had a much lower incidence of TRAEs than HDI. The most common adverse events were hyperthyroidism and rash, and there were no grade 3–5 TRAEs in the pembrolizumab group. In contrast, the incidences of myelosuppression (any grade: 93% versus 11%; grade ≥3: 7% versus 0), pyrexia (87% versus 0), nausea (47% versus 0), elevated transaminase level (AST elevation: 27% versus 11%, ALT elevation: 27% versus 11%), and fatigue (27% versus 0) were higher in the HDI group than in the pembrolizumab group. Pembrolizumab might thus be a better adjuvant treatment choice than HDI because of its more favorable safety and tolerability profile.

This study had some limitations. It was a retrospective study and thus had some information bias. In addition, the follow-up time was shorter in the pembrolizumab group compared with the HDI group. The study was also limited by the small numbers of patients in both groups; however, the rarity of pediatric melanoma means that it is difficult to conduct large or prospective studies in these patients. Furthermore, HDI might not be the best control treatment, given that it is no longer the standard adjuvant therapy for cutaneous melanoma. The study was further limited by the lack of racial diversity, given that it only included Asian pediatric patients.

In summary, pembrolizumab was associated with a lower risk of recurrence in pediatric patients with melanoma, compared with HDI, but there was no significant difference in RFS between the two treatments. Pembrolizumab also had a more favorable safety profile, consistent with its toxicity spectrum in previous studies. These data suggested that pembrolizumab might be better than HDI as an adjuvant therapy for pediatric patients with melanoma. These findings warrant further large, prospective and dedicated trials to evaluate the efficacy and safety of adjuvant pembrolizumab therapy for pediatric melanoma.

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