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Retrospective study of immune checkpoint inhibitors in pediatric malignancies, effectiveness and adverse events in Alexandria University

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Abstract

Background: Pediatric malignancies are the most fatal childhood diseases in developed countries, with survival rates reaching over 80% in high-income countries and 15-45% in low- and middle-income countries. Immune checkpoint inhibitors (ICI), including monoclonal antibodies against negative regulators of T-cell function, such as CTLA-4, Programmed Death-1 (PD-1), and PD-L1, have improved outcomes in adult cancer. Results of ICI in pediatric malignancies were all disappointing which highlight the need to improve outcomes by further studies. **Methods:** This retrospective study included 31 eligible patients from 1-20 years old to discusses the experience of Alexandria clinical oncology department and Borg el Arab pediatric oncology center, in using immune checkpoint inhibitors (ICI) in pediatric patients, with the primary goal of assessing effectiveness and the secondary is evaluating the safety profile. **Results:** Thirty one eligible patients aged 1-20 from May 2018 to May 2023, with a male-to-female ratio of 1.38:1, and the average age at diagnosis was 14.39 years old. The majority of cases (19 patients) were diagnosed with classical Hodgkin lymphoma, followed by Xeroderma pigmentosa. Pembrolizumab was the most commonly used drug. The mean PFS was 25.5 months, while the mean OS was 27 months. Side effects of ICI was found and documented in 11 patients (35.5%). Thyroiditis was found in nearly half of the patients, followed by colitis and dermatitis, all of which were grade II. Hodgkin lymphoma and Xeroderma pigmentosa showed the highest response to ICI compared to other diagnoses. **Conclusions**: immune checkpoint inhibitors are effective in pediatric malignancies, especially in Hodgkin disease and Xeroderma pigmentosa, with a very good safety profile and response rate. Further studies should be applied to verify predictive markers to know the best responders among patients.

Keywords: Pediatric malignancies, immune-checkpoint inhibitors, immune-related adverse events, side effects; immune therapy, biomarkers; prediction, diagnosis.

Introduction

Pediatric malignancies are the most fatal childhood disease in developed countries. In high-income countries, where comprehensive services are generally accessible, survival rate reaches more than 80 %, while in low- and middle-income

countries (LMICs), an estimated 15-45% of pediatric cancer patients are cured.[1] In Egypt, Five-year overall survival (OS) was 72.1% for all cancers combined, while the survival trends increased significantly from 69.6% to 74.2% between 2007-2012 and 2013-2017.[2]

In recent years, the use of immune checkpoint inhibitors (ICIs) has brought about a significant change in the treatment of various types of cancer.[3,4] The mechanism of action of ICIs involves the inhibition of specific receptors in the immune system, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed death cell protein 1 (PD-1), and PD ligand 1 (PD-L1). These inhibitory pathways are blocked by ICIs, leading to an enhanced response by T-cells to eliminate tumor cells. However, this activation of the immune system can also result in a range of adverse effects known as immune-related adverse events (irAEs),[5] which resemble traditional autoimmune disorders. From a practical perspective, an irAE can be defined as any symptom, sign, syndrome, or disease that occurs or worsens due to immune activation during the administration of an ICI, after ruling out other causes such as infections or tumor progression.[6] The occurrence of irAEs is significant as they are common and can have severe implications on the quality of life and prognosis of patients receiving ICIs.[7] Moreover, the best approach to managing irAEs while preserving the effectiveness of ICIs and the long-term survival of patients remains unclear.[8] Interestingly, patients who experience irAEs tend to have a more favorable prognosis regarding cancer.[9–11] Therefore, it is crucial to evaluate the individual risk of toxicity beforehand, enabling the early management of irAEs. This proactive approach would be beneficial for patients who are susceptible to immune-related complications but paradoxically gain more from therapy.[17]

Despite this progress, there are many challenges against the use of ICI in pediatric malignancies**.** Early trials including pediatric population that receive immune checkpoint inhibitors were disappointing regarding the response. In the early trials including pediatric solid and hematological malignancies, the objective response was nearly 5 %, most of them were Hodgkin lymphoma.[12,13,14]

The ineffectiveness of immune checkpoint inhibitors in pediatric malignancies, especially solid tumors, can be justified for many reasons. First, the PD-1, PD-L1, and PD-L2 expression are low in pediatric solid tumors; this was proved in many trials by immunohistochemistry and mRNA. Many solid tumors were included in these trials, including Ewing sarcoma, osteosarcoma, neuroblastoma, rhabdomyosarcoma, and Wilms' tumor.[15]In addition, the tumor mutational burden of pediatric malignancies is among the least if compared with other adult cancers.[16]

Our study will aim to discuss the experience of Alexandria University, namely Alexandria clinical oncology department and Borg el Arab pediatric oncology centre,

in the immune checkpoint inhibitors in the pediatric age group. To our knowledge, this is the first study in Egypt to discuss this new class of anti-cancerous treatment in this age group. We will discuss the indications given for; the type of ICI given, the safety profile and the adverse events recorded, and most importantly is the effectiveness of these drugs among various cancer types.

Materials and Methods

This retrospective study included 31 eligible patients from 1-20 years old to discusses the experience of Alexandria University, specifically the Alexandria clinical oncology department and Borg el Arab pediatric oncology center, in using immune checkpoint inhibitors (ICI) in pediatric patients, with the primary goal of assessing effectiveness and response rates, the secondary goal of evaluating safety profiles and adverse events.

We gathered pediatric patients from the Borg el Arab pediatric oncology center who have received immune checkpoint inhibitor treatment during their active treatment. Despite the small sample size of around 20 patients over the past two years, this novel treatment modality has shown promise for incurable lethal diseases, although its high cost poses a financial burden on the hospital. Nonetheless, we have successfully prescribed these drugs to our patients.

The inclusion criteria for eligible patients were as follows: age between 6 months and <18 years, confirmation of advanced, relapsed, or refractory solid tumor through histological or cytological analysis, PDL-1 expression greater than 1%, relapsed Hodgkin disease after receiving 2 or more lines of chemotherapy, or malignancies exhibiting high microsatellite instability (MSI-high) with measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

On the other hand, patients who did not meet the criteria were excluded. These included patients under the age of 6 months or over 18 years, individuals with PDL-1 expression less than 1%, and those with microsatellite stable tumors (MSS), which indicates efficient mismatch repair.

This study was encompassed the entirety of pediatric cancer patients who have received ICI as part of their treatment regimen. The focus of our discussion spanned the indications for ICI administration, the specific types of ICI employed, the safety profile and documented adverse events, as well as the crucial evaluation of drug effectiveness across different cancer types. This evaluation included an examination of response rates, encompassing complete response, partial response, stable disease, and progressive disease.

The immune checkpoint inhibitors utilized in this study included nivolumab, administered at a dosage of 2 mg/kg every 2 weeks, and pembroluzomab, administered at a dosage of 3 mg/kg every 3 weeks. These drugs may be administered either as standalone treatments or in combination with chemotherapy.

The pathological specimens for the patients are already available before the treatment was prescribed; most of them were reviewed under consultation of pathology department in Alexandria University. The PDL-1 expression and the MSI status were done by immunohistochemistry.

All enrolled patients were undergoing the following procedures: Thorough documentation of medical history and comprehensive clinical examination. Careful documentation of pathology findings. Weekly assessment of each patient throughout the course of ICI treatment, followed by monthly assessments for three months post-treatment, with a specific focus on acute toxicity. These assessments were documented in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) v4.[18] Clinical assessments every three months for duration of two years to evaluate both effectiveness and toxicity. Thorough assessment and documentation of any symptomatic late toxicity, also in accordance with CTCAE v4.[18] By adhering to these rigorous protocols, we were aimed to comprehensively evaluate the safety and effectiveness of ICI treatment in pediatric cancer patients, thus contributing to the body of knowledge in this field.

Pathological Examination

A. Macroscopic examination

The macroscopic features of the specimens were obtained from the pathology reports archived at the pathology department, Faculty of Medicine, University of Alexandria. It includes the type of specimen, tumor site, size, and the macroscopic extent of the tumor.

B. Histopathological examination

The formalin-fixed paraffin-embedded tissue blocks were cut into five micron-thick sections, stained with haematoxylin and eosin (H&E) stain and examined under the light microscope.

Categorical variables were examined utilizing Chi-square tests. PFS curves were computed utilizing the Kaplan–Meier technique, while the two-sided log-rank test was employed to assess disparities. SPSS 25.0 were employed for statistical analyses. A two-sided p value < 0.05 was deemed statistically significant.

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Results

Patients' characteristics

In our research, we included 31 eligible patients aged 1-20 from May 2018 to May 2023. The majority of the participants were male, with a male-to-female ratio of 1.38:1, and the average age at diagnosis was 14.39 years old. The majority of cases (19 patients) were diagnosed with classical Hodgkin lymphoma (61.3%), followed by Xeroderma pigmentosa in 5 patients (16.1%); the remaining 7 patients had a variety of other diagnoses including non-Hodgkin lymphoma, grey zone lymphoma, primary mediastinal B cell lymphoma, malignant melanoma, nasopharyngeal carcinoma, thymic carcinoma and atypical Teratoid rhabdoid tumor (ATRT) as shown in Table 1.

Table 1. Distribution of the studied cases according to demographic data

Demographic criteria	**The studied cases (n= 31)**	
Age at diagnosis (years)	Min. – Max.	5.0 – 20.0
	Mean ± SD.	14.39±3.92
	Median (IQR)	15.0 (12.0 – 17.50)
Sex distribution	Male 18 (58.1%)	Female 13(41.9%)
Diagnosis	**No.**	**%**
Classic Hodgkin lymphoma	19	61.3
Non Hodgkin lymphoma	1	3.2
Grey zone lymphoma	1	3.2
Xeroderma pigmentosa	5	16.1
Nasopharyngeal carcinoma	1	3.2
Thymic carcinoma	1	3.2
Primary mediastinal B cell lymphoma	1	3.2
Melanoma	1	3.2
Atypical Teratoid rhabdoid tumors	1	3.2

The prior lines and modalities of treatment

In our study, the use of immune checkpoint inhibitors as a first line of treatment was limited to only four patients (12.9%), while the majority of patients (87.1%) received the inhibitors after chemotherapy. Among those who received the inhibitors after chemotherapy, the majority had received 1-3 prior chemotherapy lines, while a small number had received more than 3 prior lines. Additionally, a limited number of

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patients underwent testing for programmed death ligand (PDL-1) and microsatellite instability (MSI), with varying results as represented in Table 2.

Table 2. Distribution of the studied cases according to treatment lines and modalities of treatment

The prior lines and modalities of treatment	The studied cases (n= 31)	
	No.	%
Treatment lines		
1st line	4	12.9
Subsequent lines	27	87.1
No. of Prior chemotherapy lines		
0	4	12.9
1	7	22.6
2	9	29.0
3	6	19.4
4	4	12.9
7	1	3.2
None (0)	4	12.9
1 – 3	22	71.0
>3	5	16.1
PDL 1 test		
Not done	27	87.1
Yes	4	12.9
If Yes; Percentage of pdl-1 (n = 4) Not <50%	1	25.0
>50%	3	75.0
MSI test		
No	26	83.9
Yes [all Deficient]	5	16.1

The immune checkpoint inhibitor received in the study

Pembrolizumab (Keytruda) was given to most of the patients, while nivolumab was given to only a few. One patient received both drugs. Some patients received chemotherapy with the ICI. The majority of patients received up to 4 cycles. Most patients had a complete or partial response to the ICI. Initial progressive disease was

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seen in a small number of patients. The ICI took less than 2 months to have an effect. The mean time for the initial response was 2 months. The mean progression-free survival was 25.5 months, while the mean overall survival was 27 months, see Table 3 and Figure 1.

Table (3): Distribution of the studied cases according to Immunotherapy

The Immunotherapy	The studied cases (n= 31)	
	No.	**%**
Immunotherapy		
Keytruda	27	87.1
Nivolumab	3	9.7
Both	1	3.2
Chemotherapy combination		
No	14	45.2
Yes	17	54.8
No of cycles		
0 – 4 cycles	19	61.3
5 – 8 cycles	7	22.6
>8 cycles	5	16.1
Initial response to ICI		
CR	18	58.1
PR	8	25.8
PD	5	16.1
Time to response (months)		
≤2	24	45.2
>2	7	54.8
	Mean	**% End of study**
Progression free survival	25.45	63.3%
Overall Survival	27.08	70.5%

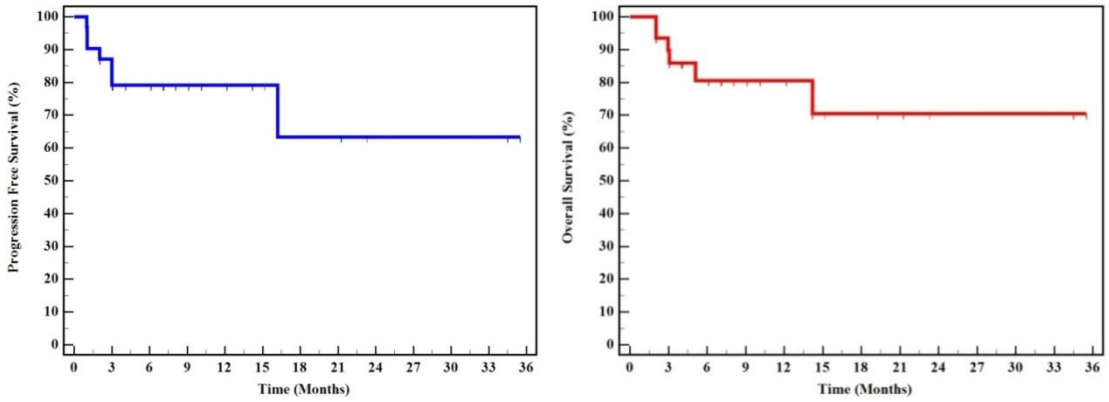

Figure 1. Kaplan-Meier survival curve for progression free survival and overall survival (n = 31)

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Lines of treatment used after ICI

By the end of the study follow-up, three patients continued with the ICI treatment, while 28 patients stopped. The main reason for stopping was achieving complete response in over half of the cases. Progression was the second cause of stopping in 7 cases. Only 2 cases stopped after reaching stable disease, and four patients stopped due to delays in bone marrow transplantation and drug supply shortage. Surprisingly, after re-introducing the anti PD-1 immune checkpoint inhibitors, 4 cases regained the response, with 2 achieving complete response and the others achieving partial response as shown in Table 4.

Table 4. Distribution of the studied cases according to Lines of treatment used after ICI

Lines of treatment used after ICI	No.	%
Lines ICI after		
Unknown	3	9.7
No	5	16.1
Yes	23	74.2
If yes (n = 23)		
Autologous BM transplantation	17	73.9
Other	3	13.0
Brentuximab vedotin	3	13.0
Radiotherapy	3	13.0
Surgery	3	13.0
Chemotherapy	4	17.4
If yes, reason for further lines		
Consolidation	19	82.6
Progression	4	17.4
Reason for stopping		
CR	19	61.3
SD	2	6.5
PD	7	22.6
Ongoing	3	9.7
Re-challenge after stoppage		
No	27	87.1
Yes	4	12.9
Response after re-challenge		
CR	2	50.0
PR	2	50.0
PD	0	0.0
SD	0	0.0

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Immune related adverse events (irAE)

In our study, and during the regular follow up, side effects of ICI was found and documented in 11 patients (35.5%). The most common irAE found was thyroiditis, found in nearly half of the patients (54.4%); all of which were grade II and didn't require dose modification. The 2nd most common adverse events were colitis and dermatitis, with 27.3% incidence for each. Pneumonitis was found in 2 patients, while fatigue and arthritis were found in one patient each. Hepatitis and myopathy were not documented in any of our cases as represented in Table 5.

Table 5. Distribution of the studied cases according to side effects

Side Effects	No.	%
Lines ICI after		
No	20	64.5
Yes	11	35.5
If yes (n = 11)		
Fatigue	1	9.1
Myopathy	0	0.0
Arthritis	1	9.1
Hepatitis	0	0.0
Colitis	3	27.3
Pneumonitis	2	18.2
Thyroiditis	6	54.5
Rash	3	27.3
Grade (n = 11)		
I	2	18.2
II	5	45.5
III	3	27.3
IV	1	9.1
No	20	64.5
I/II	7	22.6
III/IV	4	12.9
Cause of death (n = 6)		
Progression of disease	4	66.7
Complication following BM transplant	2	33.3

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Prognostic and predictive factors affecting progression free survival and overall survival

1. *The impact of histopathological diagnosis on survival*

Regarding the prognostic and predictive factors in our study, patients with classical Hodgkin lymphoma and Xeroderma pigmentosa showed the highest response to ICI compared to other diagnoses. These patients had better average progression-free survival (33.7 and 15.5 months, respectively). Patients with classical Hodgkin lymphoma specifically had significantly better average PFS than other patients, with a P-value of 0.001. Overall survival was also statistically improved in patients with classic Hodgkin lymphoma and Xeroderma pigmentosa, with average OS reaching 29.5 and 23.3 months, respectively. The P-values were 0.004 and 0.045; see Table 6 and Figure 2.

Table 6. Kaplan-Meier survival curve for progression free survival and overall survival with diagnosis

	Mean	% End of study	Log rank	
			χ^2	P
Diagnosis				
Classic Hodgkin lymphoma	33.69	94.7%	12.893*	0.002*
Xeroderma pigmentosa	15.56	37.5%		
Others	5.50	28.6%		
Diagnosis				
Classic Hodgkin lymphoma	29.48	75.0%	11.482*	0.003*
Xeroderma pigmentosa	23.30	100.0%		
Others	6.28	26.8%		

Pair wise comparison	Classic Hodgkin lymphoma	Xeroderma pigmentosa	Others
Classic Hodgkin lymphoma			
Xeroderma pigmentosa	0.113		
Others	0.001*	0.104	
Classic Hodgkin lymphoma			
Xeroderma pigmentosa	0.421		
Others	0.004*	0.045*	

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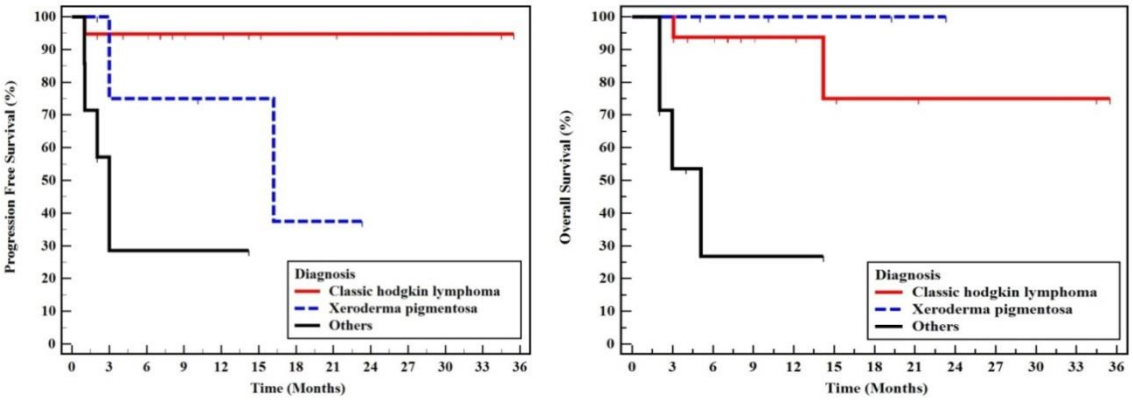

Figure 2. Kaplan-Meier survival curve for progression free survival and overall survival with diagnosis.

The impact of PDL-1 testing, MSI test, time to initial response, and receiving further lines after stopping ICI and its percentage on the survival

Table 7. Kaplan-Meier survival curve for progression free survival and overall survival with PDL-1 test, MSI test, time to initial response, and receiving further lines after stopping ICI

	Mean	% End of study	Log rank	
			χ^2	P
PDL-1 test				
Not done	28.00	70.0%	19.170*	<0.001*
Yes	1.76	25.0%		
PDL-1 test				
Not done	31.48	83.5%	32.335*	<0.001*
Yes	3.03	0.0%		
MSI test				
No	28.71	79.9%	0.295	0.587
Yes [all Deficient]	15.56	37.5%		
MSI test				
No	25.32	64.1%	1.361	0.243
Yes [all Deficient]	23.30	100.0%		
Time to response (months)				
≤2	21.72	48.6%	2.689	0.101
>2	34.50	100.0%		

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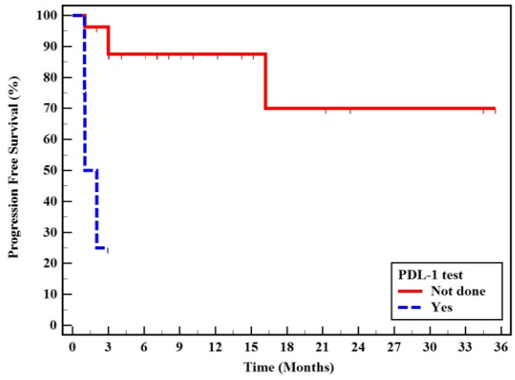
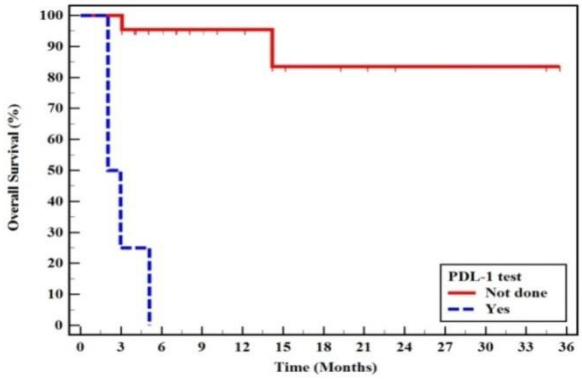
Time to response (months)				
≤2	27.00	73.6%	0.418	0.518
>2	27.73	66.7%		
Lines ICI after				
No	4.05	20.0%	18.964*	<0.001*
Yes	28.98	72.7%		
Unknown	2.033	100.0		
Lines ICI after				
No	7.11	40.0%	7.781*	0.020*
Yes	29.38	76.4%		
Unknown	2.03	100.0		

Pairwise comparison	**No**	**Yes**	**Unknown**
No			
Yes	<0.001*		
Unknown	0.124	0.718	
No			
Yes	0.007*		
Unknown	0.237	–	

In our study, the PDL-1 test had poor prognostic and predictive value for the response to ICI. Patients who did the test had shorter PFS and OS compared to those who didn't. The difference in PFS and OS was statistically significant. The MSI test had no impact on PFS or OS. The difference in PFS and OS between patients who did the MSI test and those who didn't was not statistically significant. For patients who received further lines after ICI, PFS was significantly improved in those who underwent autologous BM transplantation. Overall survival was improved in these patients but without statistical significance; see Tables 7 and 8, and Figures 3 and 4.





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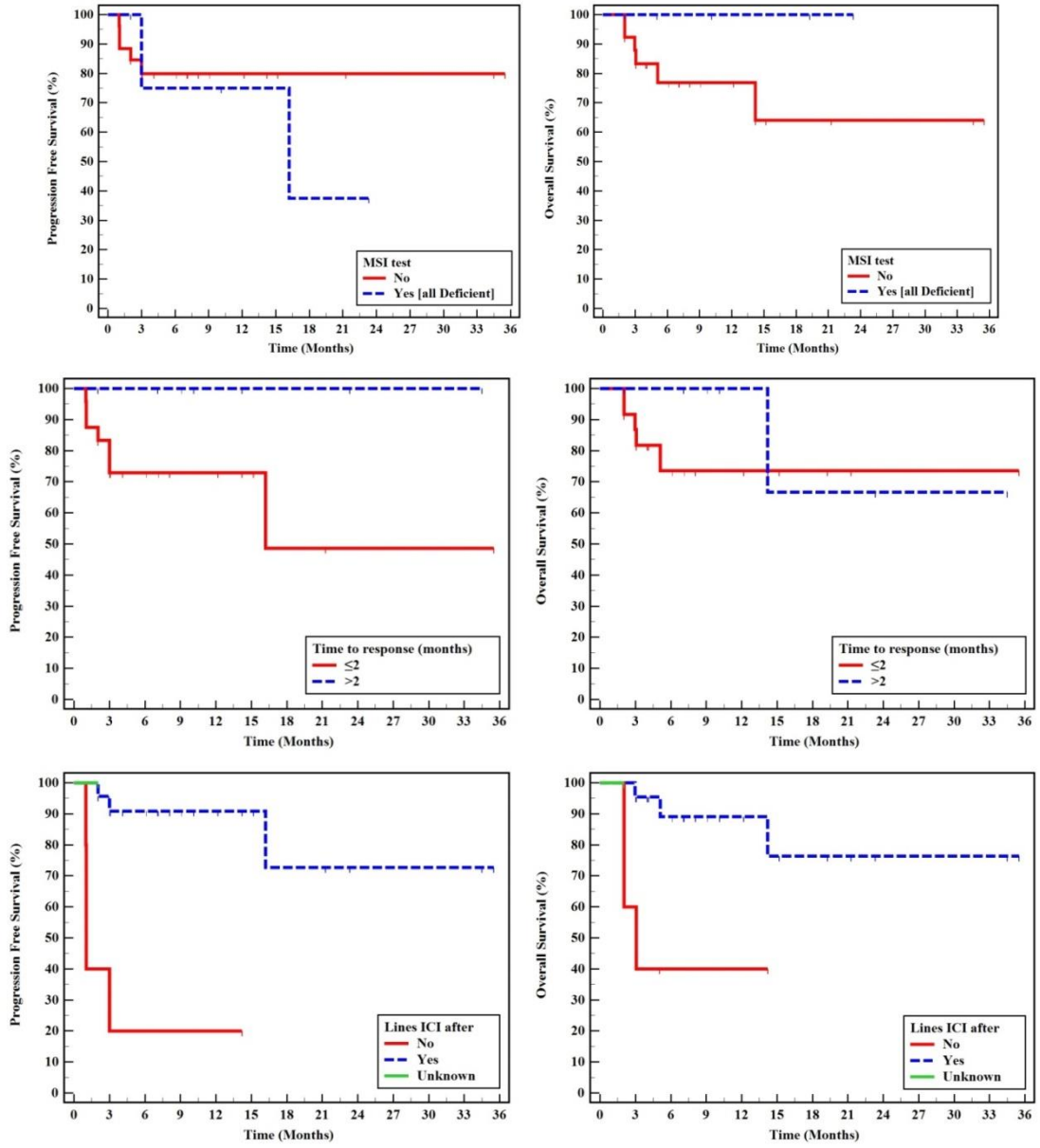

Figure 3. Kaplan-Meier survival curve for progression free survival and overall survival with PDL-1 test, MSI test, time to initial response, and receiving further lines after stopping ICI.

The impact of autologous BM transplantation after ICI and side effects on survival.

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Table 8. Kaplan-Meier survival curve for progression free survival and overall survival with autologous BM transplantation and side effects

	Mean	% End of study	Log rank	
			χ^2	P
Autologous BM transplantation				
No	14.01	33.3%	7.036*	0.008*
Yes	35.50	100.0%		
Autologous BM transplantation				
No	19.66	80.0%	0.019	0.891
Yes	29.47	75.0%		
Side effects				
No	30.10	84.0%	1.995	0.158
Yes	11.99	0.0%		
Side effects				
No	27.33	70.3%	0.006	0.941
Yes	15.37	74.1%		

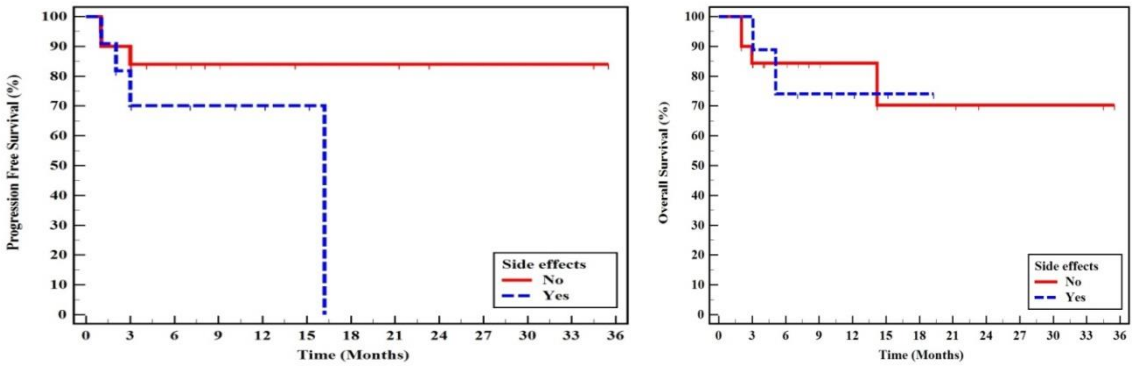

Figure 4. Kaplan-Meier survival curve for progression free survival and overall survival with autologous BM transplantation and side effects.

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Discussion

This study is the first to describe the effectiveness and safety of immune checkpoint inhibitors in pediatric cancers in Egypt and the Middle East. The number of patients (31 patients) is comparable to a larger study on pembrolizumab in pediatric cancers, which included 155 patients from 30 hospitals and 11 high-income countries.

Clinical trials focused solely on pediatric cancer patients are extremely limited in the existing literature, with only a small number of trials specifically targeting the pediatric age group under 21 years old [19,20]; of these trials, only four have published interim results without testing any predictive markers for immune checkpoint inhibitors response, unlike our study.[21, 22, 23, 24]

The male to female ratio in our study was slightly higher compared to other trials, with 58% males and 42% females. The median age at diagnosis was 15 years old, which was slightly older than the main studies of pembrolizumab and nivolumab. The most common diagnosis in our study was Hodgkin lymphoma, which primarily affects adolescents and young adults.

In over half of the cases, the most common histopathological diagnosis was relapsed classical Hodgkin lymphoma, followed by MSI high skin cancers in Xeroderma pigmentosa. These percentages were significantly higher compared to the largest trial for pembrolizumab in pediatric cancer patients.[21]

The remaining patients were diagnosed with various conditions including non-Hodgkin lymphoma, grey zone lymphoma, primary mediastinal B cell lymphoma, malignant melanoma, nasopharyngeal carcinoma, thymic carcinoma, and atypical teratoid rhabdoid tumor. In three of these patients, the PDL-1 test showed a result of more than 50%.

In our study, only a small percentage of patients received immune checkpoint inhibitors (ICI) as a first-line treatment, while the majority received ICI after chemotherapy. Most trials and FDA[25,26,27] approvals for ICI in pediatric malignancies are for relapsed/refractory diseases, with the use of ICI as a first-line treatment still under clinical trials. In one trial, pembrolizumab showed promising results in classical Hodgkin lymphoma patients who were slow early responders to front-line chemotherapy. The majority of patients in our study received pembrolizumab, possibly due to its availability and previous research on its use in pediatric and relapsed Hodgkin disease.[28]

The use of combination chemotherapy with ICI has been explored in various trials for relapsed Hodgkin disease. One such trial, CheckMate744 [29], studied the effectiveness of nivolumab plus Brentuximab vedotin (BV) followed by BV plus bendamustin for patients with suboptimal response. The trial showed a 59% complete

metabolic response rate after induction and a 91% one-year progression-free survival rate. Another study, KEYNOTE-667,[30] evaluated pembrolizumab plus chemotherapy in slow early responders with classical Hodgkin lymphoma, showing promising results with PET negativity reaching 64 to 71% in late response assessment.

After the first assessment; which is usually done after 2-3 cycles, complete response (CR) was achieved in eighteen patients 58%, While 8 patients (25.8%) had partial response (PR). Initial refractory progressive disease was seen in only 5 patients (16.1%) who had received ICI in the study.

At the end of the study, the mean progression free survival- which was defined as the time from initiation of treatment to the occurrence of disease progression or death- reached 25.5 months, while the mean overall survival-defined as the time from initiation of treatment to the death from any cause- was 27 months.

None of the other studies reported the combined results for all patients, possibly due to the significant variation in response to ICI between classic Hodgkin disease and other lymphomas or relapsed solid tumors. Our study will discuss and compare the results of different tumor types to existing literature. Initial response to ICI was observed within 2 months in 77.4% of cases, while a smaller proportion took longer to respond (22.6%). The average time for the initial response was 2 months, which is consistent with most trials involving adults but not specified in trials with pediatric patients. After discontinuing ICI, 74.2% of patients required further treatment, with autologous bone marrow transplantation being the most common approach. Consolidation treatment was the primary reason for post-ICI therapy in 82.6% of cases, while treatment after disease progression was needed in the remaining 17.4%. Although complete response can be achieved in relapsed Hodgkin disease, autologous bone marrow transplantation remains the standard of care. Retreatment with ICI after discontinuation has been studied in adult trials but not in pediatric patients. In our study, due to delays in transplantation and drug supply, four Hodgkin disease patients experienced disease relapse. These patients were reintroduced to anti PD-1 ICI and achieved response, with two cases reaching complete response and the others achieving partial response. No discontinuation was due to severe immune-related adverse events. The effectiveness of retreatment with pembrolizumab was previously investigated in an adult trial for relapsed/refractory classical Hodgkin lymphoma, with an overall response rate of 73.7% and complete and partial response rates of 36.8% each.[31,32,33]

The disease control rate (DCR)after retreatment in our study was 100%, with CR and PR each at 50%. The reasons for discontinuation varied, but due to the small sample size of only 4 patients, these results should be confirmed by larger studies.[34, 35] In a meta-analysis on retreatment with ICI in non-small cell lung cancer, Cai et al.[36] reported an

ORR of 34% and a DCR of 71%, which did not significantly differ from initial ICI treatment.

Among 11 patients, immune related adverse events (irAEs) were observed in 35.5%, with thyroiditis being the most common (19.3%). Colitis and dermatitis each had an incidence of 9.6%. Pneumonitis, fatigue, and arthritis occurred in fewer patients. The grading of irAEs revealed grade II as the most common, followed by grade III, I, and IV. No fatal adverse events were observed in our study. However, the incidence of irAEs differed slightly compared to other trials, indicating the need for further investigation.

Among the various factors examined in our study, the histopathological diagnosis emerged as the most reliable prognostic and predictive factor for the response to immune checkpoint inhibitors (ICI). Classical Hodgkin lymphoma and Xeroderma pigmentosa patients exhibited a superior response to ICI compared to other diagnoses. Our trial involved 19 patients with relapsed classic Hodgkin lymphoma, who demonstrated significantly better mean progression-free survival (PFS) of 33.7 months and mean overall survival (OS) of 29.5 months, with P-values of 0.001 and 0.004, respectively. The 36-month PFS and OS rates were both 95%.

Xeroderma pigmentosa, a genetic disorder, occurs at different frequencies across populations. Molecular analysis has identified eight subtypes, where deficiencies in nucleotide excision repair are associated with seven subtypes (XP-A through G), and defects in translation DNA synthesis are associated with the eighth group (XP-V). Our study, which included the largest number of Xeroderma pigmentosa patients receiving ICI, found that partial response was achieved in 80% of patients, with only one patient progressing on ICI. The mean number of cycles was 9.6, with a mean progression-free survival of 15.5 months and an improved overall survival of 23.3 months. Published case reports for similar cases[37-39] showed similar results, with partial response being the most common outcome.

In our study, the PDL-1 test was performed on four cases, all of which were positive for tumors other than Hodgkin disease. Three of these cases had a PDL-1 test result of more than 50%. However, unlike adult malignancies, PDL-1 positive patients did not respond well to immune checkpoint inhibitors (ICI). The patients who tested positive for PDL-1 had significantly shorter progression-free survival (PFS) and overall survival (OS) compared to those who did not undergo the test. Similarly, the MSI test, which was conducted on Xeroderma pigmentosa patients, did not predict a better response to ICI. However, the mean PFS and OS were similar to those observed in the KEYNOTE-158 trial.[40] Patients who underwent autologous bone marrow transplantation after ICI treatment experienced significantly improved PFS compared to those who did not undergo transplantation. While overall survival was also

improved in these patients, the difference was not statistically significant. These findings align with a large retrospective trial that demonstrated the importance of responsiveness to ICI, rather than chemotherapy, in predicting outcomes after autologous transplant.

The relationship between irAE and response to immune checkpoint inhibitors ICI is still uncertain. Our study found that patients without irAE had better progression-free survival (PFS) and overall survival (OS) compared to those with irAE, with mean PFS and OS of 30 and 27 months for the former and 12 and 15.3 months for the latter. However, these results were not statistically significant. Further research is needed to confirm the predictive value of irAE.[41]

The field of ICI-related toxicity is rapidly evolving, with a significant increase in publications on potential irAE biomarkers. However, no biomarkers have been validated for clinical use, except for routine laboratory testing. Known biomarkers are unable to predict toxicity in most patients, although they may be useful in certain clinical scenarios. The complexity of irAE pathogenic mechanisms further complicates the identification of applicable biomarkers. A pragmatic approach would be to develop cross-sectional risk toxicity scores that include accessible and understandable biomarkers. Currently, there are no multi-factor prediction models combining patient characteristics with easily measurable biomarkers. Longitudinal data on biomarker fluctuations and the incorporation of more sophisticated diagnostic tools may provide a more reliable approach. Research on artificial intelligence, big data, and machine learning shows promise in creating predictive models of toxicity.

Despite being the first trial to investigate predictive biomarkers in immune checkpoint inhibitors for pediatric malignancies, it has some pitfalls. First, the sample size of the patients is not big, mainly due to the limited resources to provide the ICI to all indicated patients and the limited indications for the ICI in pediatric oncology till now. To expand this trial on a larger scale this will verify our results and help to select which patients that get the maximum response from ICI. In addition, the trial is single arm and not randomized controlled one.

Conclusions

The study, while limited to a single center in a low middle income country, included 31 patients and showcased comparable results to larger trials in high income countries. The majority of patients had relapsed classical Hodgkin lymphoma, with significant responses observed in this subgroup. The study also highlighted the significance of histopathological diagnosis in predicting response to immune checkpoint inhibitors, with classical Hodgkin lymphoma and Xeroderma pigmentosa

showing the best outcomes. Furthermore, the study emphasized the importance of combination therapies, particularly with chemotherapy in enhancing response rates.

The results also underscored the impact of autologous bone marrow transplantation on improving progression-free survival. Additionally, the study identified immune related adverse events, with thyroiditis being the most common, and their potential correlation with treatment outcomes. Further analysis revealed the predictive value of certain tests such as PD-L1 and MSI, with varying responses observed in different patient subgroups. In immunologically 'cold' childhood cancers, there appears to be a lack of neoantigens and naturally occurring tumor-reactive effector lymphocytes. There is a critical need for enhanced understanding of the immune microenvironment and immune subtypes for pediatric cancers in the absence of high neoantigen burden.

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