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Role of pembrolizumab in relapsed Hodgkin lymphoma patients

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Abstract

About 10–15% of patients with early-stage and 15-30% with relapsed Hodgkin lymphoma after primary conventional treatment. Despite the approval of novel therapies, autologous stem cell transplantation (ASCT) remains the standard of care in these patients. However, up to half of transplanted individuals may relapse. Pembrolizumab is an FDA-approved monoclonal antibody directed against programmed cell death protein 1 (PD-1), it has received approval for the treatment of solid cancer and showed increased progression-free survival in high-risk patients with relapsed Hodgkin lymphoma receiving autologous stem cell transplantation. This study aims to investigate the role of relapsed Hodgkin lymphoma after using Pembrolizumab. This study was conducted for 80 patients with relapsed Hodgkin lymphoma who received Pembrolizumab and 50 patients had completed treatment with 40% complete response.
In conclusion, Pembrolizumab showed a good response in patients with relapsed Hodgkin lymphoma.

Keywords: Pembrolizumab; Relapsed Hodgkin lymphoma; ASCT

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Introduction

Pembrolizumab, as an IgG4 subclass antibody, is preferred over other subclasses as it only induces weakly the complement and cell activation due to low affinity to C1q and Fc receptors. It binds with high affinity to the cell surface receptor programmed cell death protein 1 (PD-1) and it antagonizes its interaction with its known ligands PD-L1 and PD-L2. In normal circumstances, the binding of the ligands of PD-1 to the receptor inhibits the TCR-mediated T cell proliferation and cytokine production [1]. This inhibitory signal seems to be essential for self-tolerance, collateral damage minimizing after immune response against a pathogen and maternal tolerance to fetal tissue [2]. Therefore, the binding of pembrolizumab to PD-1 prevents the inhibitory pathway causing a physiological shift to immune reactivity and enhancing tumor immune-surveillance and anti-tumor immune response [3]. Hodgkin lymphoma (HL) is the most common lymphoma affecting the young population, with over 9,000 estimated new cases of HL

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in the US in 2014. The incidence of HL is bimodal with the highest incidence at age 15 to 34 years, and a second peak in those older than age 60 years [4]. Despite the favorable outcome for most patients, approximately 25 % of patients will experience a relapse or be refractory to initial therapy. For these patients, only 50 % will be cured with standard salvage therapies [5]. Major challenges for the management of these relapsed patients include: improving risk stratification, the sequencing of standard therapy with promising new agents, and the role of consolidation strategies such as hematopoietic stem cell transplant for high-risk remission, both upfront and at the time of relapse [6].

According to retrospective and prospective as well as randomized studies, HDC followed by auto-SCT can rescue 30% to 80% of relapsed/refractory HL patients [7].

In the BNLI trial relapsed patients were treated with conventional dose mini-BEAM (carmustine, etoposide, cytarabine, and melphalan) or high-dose BEAM with auto-SCT. Both event-free survival (EFS) and progression-free survival (PFS) showed significant differences in favor of BEAM plus transplant. In the GHSG trial, patients who relapsed after chemotherapy were randomly given four courses of mini-BEAM+dexamethasone (dexa-mini-BEAM) or two courses of dexa-mini-BEAM followed by BEAM and auto-SCT [8]. Freedom from treatment failure (FFTF) in 3 years was significantly better for patients given BEAM and auto-SCT (55%) than for those on dexa-mini-BEAM (34%). Overall survival (OS) of patients given either treatment did not differ significantly [9]. Recently, the GHSG group evaluated the impact of sequential HDC before myeloablative therapy. Patients with histologically confirmed, relapsed HL were treated with two cycles of dexamethasone, cytarabine, and cisplatin, and those without disease progression were then randomly divided between standard and experimental treatment arms [10]. In the standard arm, patients received myeloablative therapy with BEAM followed by auto-SCT. In the experimental arm, patients received sequential cyclophosphamide, methotrexate, and etoposide in high doses before BEAM. Mortality was similar in both arms (20% and 18%). With a median observation time of 42 months, there was no significant difference in terms of FFTF and OS between arms. FFTF in 3 years was 62% and OS was 80%. Results demonstrated that sequential HDC did not improve outcome and was associated with more adverse events and toxicity.

BEAM is considered the gold standard conditioning regimen for auto-SCT. However, due to drug constraints of carmustine, this drug is often replaced by a variety of agents, including fotemustine, bendamustine, and thiotepa [11].

Recent author published a retrospective analysis of 175 patients with HL who did not undergo remission after induction therapy and results were reported to the European Group for Bone Marrow Transplantation (EBMT). The 5-year actuarial OS and PFS rates were 36% and 32%, respectively, and results were very similar to those reported from single-institution series and from the Autologous Blood and Marrow Transplant Registry (ABMTR) [12]. The ABMTR series includes 122 patients with HL who have never achieved remission. The definition of failure to achieve remission differs from that in the EBMT series, in that it includes only those patients

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who had a documented disease progression or tissue confirmation of persistent disease in residual radiographic abnormalities [13]. With a median follow-up of 28 months from the date of auto-SCT, the 3-year actuarial PFS and OS rates in this series were 38% and 50%, respectively. The GELTAMO Cooperative Group presented the results of 62 patients treated with an auto-SCT for refractory HL. One-year transplant-related mortality (TRM) was 14%. The response rate in 3 months after auto-SCT was 52%. Actuarial 5-year time to treatment failure (TTF) and OS were 15% and 26%, respectively. The presence of B symptoms at auto-SCT was the only adverse prognostic factor significantly influencing TTF. The presence of B symptoms at diagnosis, MOPP-like regimens as first-line therapy, bulky disease at auto-SCT, and two or more lines of therapy before auto-SCT adversely influenced OS [14].

Tandem auto-SCT for HL has been evaluated in a small number of studies and in the most recent guidelines from the American Society for Blood and Marrow Transplantation it is not recommended, although further studies may be warranted in high-risk patients [15].

This study aims to investigate the role of relapsed Hodgkin lymphoma after using Pembrolizumab.

Patients and Methods

This part is concerned with the collection of clinical characteristics data obtained from the patient's file through the retrospective database, which includes (first diagnosis, first-line treatment, second-line treatment, type of disease after second line, Pembrolizumab protocol, and patient response after Pembrolizumab). It was used to determine patients' outcomes to Pembrolizumab medication in pre-test post-test, it was constructed and reviewed by using the most recent and relevant literature and consists of three parts:

I- **Histological:** to determine the subtype of CHL.

II- **Radiological:** to determine patient response such as (PET/CT, or CT-Scan with contrast).

III- **Laboratory test:** to determine the effect of Pembrolizumab, (hemoglobin, white blood cell, platelet, lactate dehydrogenase, erythrocyte sedimentation rate, and serum albumin) in pre-test and post-test are used.

Used for observing the side effects of Pembrolizumab for each patient at the hematology clinic during and after Pembrolizumab administration.

The patient received Pembrolizumab (Keytruda) at 200 mg / 3 weeks' intravenous infusions for 4-6 cycles according to their response. Pembrolizumab treatment aimed to achieve at least a partial response.

The Lugano response criteria recommend the Deauville five-point scale for reporting response by FDG PET-CT (55):

- **Deauville-1**: no uptake or no residual uptake (when used interim)

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- **Deauville-2**: slight uptake, but below blood pool (mediastinum)
- **Deauville-3**: uptake above mediastinal, but below or equal to uptake in the liver
- **Deauville-4**: uptake slightly to moderately higher than liver
- **Deauville-5**: markedly increased uptake or any new lesion (on response evaluation)

▪ **Type of response**

- complete metabolic response (CMR) score of 1, 2 or 3 in nodal or extranodal sites with or without a residual mass
- partial metabolic response (PMR) score of 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size
- stable disease or no metabolic response score of 4 or 5 with no obvious change in FDG uptake

▪ **Progressive disease score**

- 4 or 5 in any lesion with an increase in the intensity of FDG uptake from baseline (and/or new FDG-avid foci consistent with lymphoma).

Lugano response criteria which recommend reporting response by CT-Scan:

Complete response:

- nodal site reduce ≤1.5 cm in longest transverse diameter (LDI) of a lesion.
- complete disappearance of radiologic evidence of disease

Partial response:

- ≥50% decrease in the sum of the product of the perpendicular diameters (PPDs) of up to six representative nodes or extranodal lesions

Stable disease:

- <50% decrease from baseline in PPDs of up to six dominants, measurable nodes, and extranodal sites.
- no criteria for progressive disease are met

Progressive disease:

1- new or increased adenopathy; an individual node must be abnormal with:

- longest transverse diameter (LDi) >1.5 cm.
- PPD increase by ≥50% from nadir.

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- longest transverse diameter (LDi) or shortest axis perpendicular to LDi (SDi) increase from nadir; the increase in LDi or SDi from nadir (the smallest recorded measurement) must be >0.5 cm for lesions ≤2 cm and >1.0 cm for lesions >2 cm.

2- splenic volume increase.

- With prior splenomegaly: increase in length by >50% of its prior increase beyond baseline; for example, splenic length increases from 15 cm (2 cm above baseline splenomegaly of 13 cm) to >16 cm (>3 cm above baseline).
- without prior splenomegaly: length increase by at least 2 cm.
- new or recurrent splenomegaly.

3- new or larger non-measured lesions.

4- recurrent previously resolved lesions.

5- new extranodal lesion >1 cm in any axis (new lesions <1 cm in any axis are included if these are “unequivocally attributable” to lymphoma).

Statistical analysis

All data were analyzed using SPSS 20.0 software (IBM Corp., Armonk, NY). Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables are expressed as numbers and percentages. Differences in baseline characteristics among the three groups were analyzed by one-way ANOVA. A *P* value of < 0.05 was considered statistically significant.

Results

Total of 30 patients were included, 27 patients who completed treatment and their response had been evaluated. Two patients were dead after one cycle of pembrolizumab. One patient lost follow up.

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Table 1.

Demographic Characteristics of Study Sample

variables		Frequency	Percent
Gender	Male	16	59.3
	Female	11	40.7
Age Group	15.00 - 24.00	9	33.3
	25.00 - 34.00	11	40.7
	35.00 - 44.00	3	11.1
	45.00 - 54.00	2	7.4
	55.00+	2	7.4
	Mean ± SD	**31.8±11.1**	
Marital status	Single	9	33.3
	Married	18	66.7
Smoking	Yes	7	25.9
	No	20	74.1
Stage of disease	stage I	2	7.4
	stage II	11	40.7
	Stage III	6	22.2
	Stage IV	8	29.6

Table (1) show that the (59.3%) of study participants were male and females were **40.7%** of patients. The mean age of patients was 31.8 ± 11.1 years (range **17 – 60** years). Related to marital status, the table (1) showed that majority of patients were married **(66.7%),** and majority of patients were nonsmokers **(74.1%)**. Regarding to stage of disease; (40.7%) of patients with stage two.

Table 2.

First Line Treatment of the Study Sample

Variable	Rating	Frequency	Percent
First line treatment	ABVD	26	96.3
	BEACOPP	1	3.7
	Total	27	100.0
radiotherapy1	Yes	2	7.4
	No	25	92.6
	Total	27	100.0

Table (2) demonstrate that first line treatment was (ABVD) for 26 (96.3%) patients and BEACOPP for 1 (3.7%) patients. The radiotherapy was done for 2 (7.4%) patients only.

Table 3.

Salvage Therapy of the Study Sample

Variable	Rating	Frequency	Percent
Salvage therapy	GDP	20	74.0
	ICE	24	88.8
	DHAP	6	22.2
	ESHAP	1	3.7
	GCD	3	11.1
	Nivolumab	6	22.2
	Brentuximab	6	22.2
	Total	27	100.0
Radiotherapy 2	Yes	0	0
	No	27	100.0

Table (3) show that salvage therapy was given for all relapsed and /or refractory patients in different frequencies, 20 (74%) of patients received GDP, 24 (88.8%) received ICE.

Table 4.

Number of Salvage Therapy

Variable	Numbers of lines	Frequency	Percent
Number of salvage therapy	1	5	18.5
	2	11	40.7
	3	6	22.2
	4	4	14.8
	5	1	3.7
	Total	27	100

Table (4) demonstrates that 5 (18.5%) of patients received 1 salvage, 11 (40.7%) of patients received 2 salvage, 6 (22.2%) of patients received 3 salvage, 4 (14.8%) of patients received 4 salvage, and only one (3.7%) patients received 5 salvage therapy.

Table 5.

Number of pembrolizumab cycles

Variable	Number of cycles	Frequency	P
Number of pembrolizumab cycles	Four cycles	19	
	Six cycles	8	
	Total	27	

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Regarding number of cycles, there were 19 (70.4%) of patients who had received 4 cycles of Pembrolizumab and 8 (29.6%) of patients who had received 6 cycles of Pembrolizumab.

Table 6.

Patients' response after Pembrolizumab Treatment

Variable	Type of response	Frequency	Percent
Patients' response	CR	11	40.7
	PR	4	14.8
	SD	1	3.7
	PD	11	40.7
	Total	27	100.0

Assessment of the patients' response after Pembrolizumab showed that 11 (40.7 %) of patients have complete response, 4 (14.8) patients have partial response, while 12 (44.4%) patients showed a SD/PD. Fifteen (55.5%) of patients who achieved (CR+PR) underwent Autologous BMT and 12 (44.5%) patients (SD+PD) had refractory disease and received other lines of treatment.

Table 7.

Comparison of the Biochemical Test and CBC Pre and Post Pembrolizumab

Lab. Results	Pre-Treatment	Post Treatment	P value
LDH U/L (mean ±SD)	321±54	246±62	0.001
ESR MM/1st hr.(mean ±SD)	71.2±26	29±22	0.001
Albumin g/L (mean ±SD)	3.8±0.5	4.1±0.6	0.04
Hb g/dL (mean ±SD)	11.2±1.6	12.82±1.3	0.002
WBC *10⁹/L (mean ±SD)	7703.7±3568	6718±2339	0.26
Neutrophil *10⁹/L (mean ±SD)	5518.5±3233	4488±1878	0.17
Lymphocyte *10⁹/L (mean ±SD)	1561.1±553	1664±601	0.39
Platelet *10_{12}/L (mean ±SD)	248000±122768	197303±69073	0.076

*Paired sample t test.

The biochemical test and CBC before and after Pembrolizumab showed a statistically significant decrease in LDH and ESR means, a significant increase in Albumin and Hb means, and no significant change in WBC, neutrophil, lymphocytes, and platelets counts mean

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Table 8.

Comparison of the baseline biochemical test and CBC based on response

	n= CR+PR	n= SD+PD	P value*
LDH (mean ±SD)	332.6 ± 52.6	306.9 ± 55.7	0.23
ESR(mean ±SD)	70 ± 28.3	72.8 ± 24.1	0.78
Albumin(mean ±SD)	3.9 ± 0.6	3.8 ± 0.5	0.53
Hb (mean ±SD)	10.9 ± 1.7	11.5 ± 1.4	0.33
WBC(mean ±SD)	7860 ± 3610	7508 ± 3665	0.81
Neutro(mean ±SD)	5616 ± 3478	5395 ± 3047	0.86
Lympho(mean ±SD)	1670 ± 618	1425 ± 449	0.26
Platelet (mean ±SD)	233066 ± 111820	266666± 137975	0.49

*Paired sample t test.

The comparison of baseline lab. results based on response did not demonstrated a significant difference in baseline lab results between CR+PR and SD+PD groups.

Table 9.

Factor associated with Patients' Outcomes

Gender			
Male	8	8	0.484
Female	7	4	
No. of Salvage			
1	3	2	
2	6	5	
3	2	4	0.761
4	3	1	
5	1	0	
Pembrolizumab cycles			
4	10	9	0.841
6	5	3	

Table (3-9) demonstrate that was no statistically significant association between gender, number of Salvage, and number of Pembrolizumab cycles and patients' responses at p-value (0.05).

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Table 10.

Pembrolizumab Side effects

Side Effect	Frequency	Percentage
Fatigue	17	62.9
Itching	4	14.8
Cough	0	0
Nausea	10	37.1
Rash	0	0
Decreased appetite	3	11.1
Constipation	0	0
Diarrhea	0	0
Arthralgia	6	22.2
Pain in extremity	5	18.5
Shortness of breath	0	0
Swelling	4	14.8
Headache	2	9.1
Vomiting	3	13.6
Chills	0	0
Myalgia	6	22.2
Insomnia	3	13.6
Abdominal pain	0	0
Back pain	0	0
Fever	0	0
Vitiligo	0	0

The most common side effect observed with Pembrolizumab was fatigue which was observed in 17 (62.9%) patients. Most toxicities observed with Pembrolizumab were (grade I- grade II). Other side effects such as (Chills, Abdominal pain, Back pain, Fever, and Vitiligo) were not observed.

Discussion

Immune evasion is a critical mechanism of malignant cell survival and relies in part on molecular signaling through the programmed cell death 1 (PD-1)/PD-1 ligand (PD-L1) axis that contributes to T cell exhaustion. In the treatment of advanced solid tumors and hematologic malignancies, immune modulatory therapy using monoclonal antibodies targeting PD-1 has shown promise in enhancing antitumor immune response [15].

The mean age of included patients was 31 years and this was in line with Chen et al study that showed median age 35 years with range from 18 – 76 years. Also, another study by Al-Froukh et al from Jordan showed that mean age of refractory HL was 29 years [16].

There was slightly higher males' percentage in this study. This was in line previously mentioned study, Al-Froukh et al from Jordan that showed males were representing 59% of their cases. The gender difference would not explain, however, the early/advanced-stage discrepancy have been observed in related to race rather than gender [17].

Regarding the pembrolizumab cycle, majority of patients received 4 cycles. A study by Chan et al that assessed the pembrolizumab for relapsed/refractory Hodgkin lymphoma they continue

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treatment with pembrolizumab for a median of 16 cycles of low dose and they concluded that low dose pembrolizumab was highly efficacious [18].

In this study, the assessment of outcomes showed that 55% of patients had achieved complete or partial response. This was consistent with the first evidence of pembrolizumab's safety and activity in relapsed/refractory cHL, which came from a phase Ib study that showed an ORR of 65 percent, with 5 patients (16%) achieving a complete response (CR) and 15 patients (48%) achieving a partial response (PR); 16 of the 20 responding patients achieved their best response at around 12 weeks. At 24 weeks, the PFS rate was 69%, and at one year, it was 46%. Interestingly, the ORR to pembrolizumab was lower in transplant-naïve patients, compared with patients who had failed autologous SCT (44% versus 73%, respectively). These results positioned pembrolizumab as an attractive immunomodulatory agent that can induce high and durable responses in heavily pretreated cHL [19].

In the phase Ib trial in relapsed/refractory cHL described above, pembrolizumab was given at a dose of 10 mg/kg every 2 weeks. However, subsequent studies found a flat exposure–response in the dose range of 2–10 mg/kg; therefore, it was concluded that a fixed dose of 200 mg every 3 weeks and weight-based dose of 2 mg/kg provide similar exposure distributions. Like other therapeutic IgG monoclonal antibodies, pembrolizumab has a low volume of distribution and a half-life of approximately 3 weeks [20].

The overall response rate was observed in 78% of their patients and this was higher that what observed in this study. The current study demonstrated the feasibility of using pembrolizumab as bridging to ASCT in around more than half of chemo-resistant RRcHL. The patients had chemo-resistant disease, which necessitated the use of pembrolizumab to restore chemo-sensitivity followed by ASCT to maintain disease remission, as substantial proportion of patients will relapse post pembrolizumab. Bridging patients to ASCT post-pembrolizumab in our center, was in line with results of a retrospective study conducted by Carreau et al., which demonstrated clearly the positive impact of using anti-PD-1 to sensitize RRcHL chemo-resistant patients toward subsequent treatment-including ASCT after anti-PD-1.

Regarding LDH, in this study, LDH showed significant decrease after pembrolizumab treatment. LDH testing is a mandatory laboratory test as it is a factor associated with disease prognosis, and response. The significant decrease in LDH came from higher percentage of response that achieved by pembrolizumab treatment, while in previously other clinical trials, increased lactate dehydrogenase levels during the treatment with pembrolizumab were reported iñ30% of patients.

Also, ESR, showed significant reduction after pembrolizumab treatment, while albumin, and hemoglobin were significantly increased after pembrolizumab treatment, and this indicated good response to pembrolizumab [21].

Fatigue was the most prevalent side effect of pembrolizumab medication in this study, with over 60% of patients reporting it. Nausea, arthralgia, and myalgia were the next symptoms to appear. Generally, in this study the adverse event of pembrolizumab was tolerable and acceptable and

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this was agreed with other studies that demonstrated most common treatment-related adverse events were hypothyroidism (16%), diarrhea (13%), and pneumonitis (10%) [22].

Pembrolizumab did not cause any new side effects or treatment-related mortality after a 2-year follow-up period. Extended follow-up validated pembrolizumab's adequate safety, antitumor efficacy, and response durability in RRcHL patients. Furthermore, independent of BV usage or sequence, the response was generally deep and durable. Also, among 210 pembrolizumab-treated patients, all of the patients had HL that was refractory or had relapsed. The most prevalent treatment-related adverse events (TRAEs) were fatigue (6.7 %), headache (6.7 %), rash (6.2 %), and nausea (5.7 %) after a median of 9 cycles [23].

Conclusions

Pembrolizumab-related adverse events were mild and tolerable in all patients, and the most prevalent adverse event associated with pembrolizumab medication was fatigue, which was reported by more than 60% of patients. Over response rate (ORR) after Pembrolizumab was (50%).

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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