

ORIGINAL ARTICLE

Clinical significance of PD-1 and PD-L1 molecules in patients with diffuse large B-cell lymphoma, not otherwise specified: Correlation with clinical and pathological findings

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Summary

Purpose: To investigate a possible chemorefractoriness mechanism of a Diffuse Large B-Cell Lymphoma (DLBCL) histological subtype, specifically of DLBCL, not otherwise specified (DLBCL, NOS), namely the effect of programmed cell death-1 (PD-1) immunoreceptor signalling, considering that the identification of additional negative prognostic factors can lead to better prognostication and therapeutic approaches.

Methods: We conducted a retrospective study of DLBCL, NOS patients, gathering their clinical features and combining them with PD-1 and its ligand (PD-L1) expression at the time of diagnosis as well as their response to treatment.

Results: No statistically significant difference was found when comparing PD-L1 positive to PD-L1 negative patients, while overall survival (OS) and duration of complete response (CR) were better for PD-L1 negative patients but the difference was not statistically significant.

Conclusions: PD-L1 expression was not found to have any prognostic value for our cohort of DLBCL, NOS patients. What is more, the number of PD-1 positive tumour infiltrating lymphocytes was not associated with PD-L1 expression neither on malignant nor on non-malignant cells.

Key words: diffuse large B-cell lymphoma, immunoevasion, PD-1 axis

Introduction

Lymphomas are malignancies of the lymphatic tissue, which is an important component of the immune system. It is therefore interesting that immune response to these malignancies varies from extremely vivid (yet ineffective, as in classical Hodgkin lymphoma, where inflammatory cells consist up to 99% of the tumour tissue) to rather weak (as seen in patients with Diffuse Large B-cell Lymphoma, DLBCL) [1,2]. The latter is the most common non-Hodgkin Lymphoma (NHL), accounting for 30-40% of these lymphomas. It belongs to high-grade lymphomas and DLBCL patients have

a 5-year progression free survival (PFS) rate of 30-91% and a 5-year overall survival (OS) rate of 33-96%, depending on several clinical and laboratory risk factors and the calculation of the corresponding revised International Prognostic Index (R-IPI) and its National Comprehensive Cancer Network analogue (NCCN-IPI) [3,4].

At the cellular and molecular level, the clinical course and prognosis of DLBCL patients appear to depend to a considerable extent on the escape of lymphoma cells from the defence mechanisms of the immune system and in particular those driven

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by T lymphocytes, which constitute the main defensive mechanism against neoplastic cells [5-10]. This is achieved by various mechanisms such as decreased production and expression of cancer antigens, production and secretion of immunosuppressive molecules, metabolic exhaustion of the immune cells, the abnormal endothelium of blood vessels that supports tumour growth, mobilization of immunosuppressant mechanisms such as regulatory T lymphocytes and last but not least, the suppression of tumoricidal lymphocytes through certain ligands [11-23].

Such an inhibitory role in the proliferation and activation of T lymphocytes and therefore in the immune surveillance and destruction of neoplastic cells is performed by Programmed cell Death-1 (PD-1) immunosuppressive receptor through its binding to 2 ligands, PD-L1 (CD274 or B7-H1) and PD-L2 (CD273 or B7-DC), all members of the B7 protein family [24]. Specifically, T cell activation induces PD-1 expression on the cell surface and phosphorylation of all inhibitory receptors. The activated PD-1 receptor then binds to Src homology 2 (SH2) - domain-containing protein tyrosine phosphatase 1 and 2 (SHP1 and SHP2) phosphatases. These phosphatases contribute to both direct suppression of proximal T-Cell Receptor (TCR) signalling and inhibition of inositol triphosphate kinase

(PI3K) and protein kinase B (PKB) activation (Figure 1) [25].

PD-1 receptor is predominantly expressed on the surface of T lymphocytes but also on B lymphocytes, natural killer cells (NK) and monocytes/macrophages, indicating that it has a more widespread immunosuppressive role than the immunosuppressant CTLA-4 receptor (Cytotoxic T-Lymphocyte Antigen 4, CD152) which is expressed only in the early phase of T lymphocytes' activation [26]. The expression of PD-L2 is restricted to tissues such as the lungs, liver and pancreas, B and T lymphocytes, macrophages, dendritic cells and some cancer cells, while PD-L1 has a wider expression as it is also detected in lymphatic and hematopoietic tissue, endothelial and parenchymal/epithelial cells after exposure to inflammatory cytokines, its role possibly being to protect non-haematopoietic tissues from excessive stimulation of immune cells [24,27-31]. PD-L1 has also been detected in several solid tumours [32-37] and its presence has been associated with disease progression and poor prognosis [36,38-53], just like the detection of PD-1 on Tumour Infiltrating Lymphocytes (TILs) [54].

This study aimed to investigate PD-1 - and PD-L1 - involving pathogenetic pathways and chemoresistance in a DLBCL subtype, namely DLBCL, Not Otherwise Specified (DLBCL, NOS), which con-

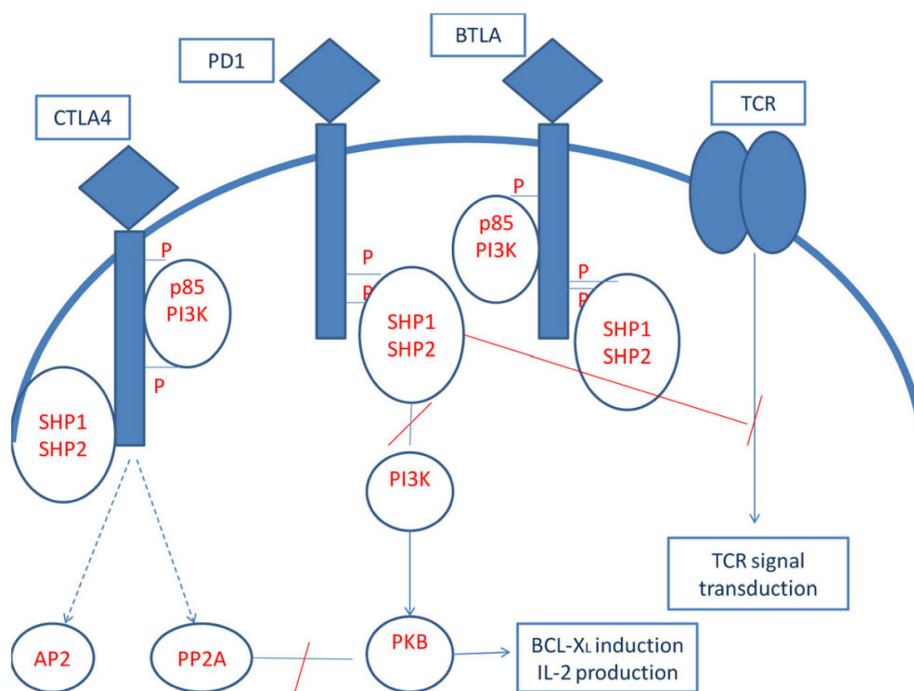


Figure 1. Immunoinhibitory pathways in T lymphocytes. AP2, Acid-binding Protein 2; BCL-XL, B-Cell Lymphoma-eXtra Large antiapoptotic protein (member of the BCL-2 family); BTLA, B- and T-Lymphocyte Attenuator; CTLA-4, Cytotoxic T Lymphocyte Antigen 4; IL-2, Interleukin-2; PD-1, Programmed cell death-1; p85, PI3K regulatory subunit; PI3K, Phosphatidylinositol 3-Kinase; PKB, Protein Kinase B; PP2A, Protein Phosphatase 2A; SHP1 and SHP2, Src Homology 2 (SH2)-domain-containing protein tyrosine Phosphatase 1 and 2; TCR, T-cell receptor

stitutes at least 25-30% of all DLBCL cases [55]. Recognition of immunohistochemical markers with negative prognostic value may lead to a better understanding of the pathophysiology of these lymphomas and more efficient treatments.

Methods

Patients

Patient cases of untreated DLBCL, NOS diagnosed between 2006 and 2018 were retrieved from our Department's medical records. All cases were diagnosed and classified according to 2008 World Health Organization criteria. Twenty-seven cases of patients with untreated DLBCL, NOS were identified. Patient demographics, clinical data, treatment and outcome information were available in all cases. Clinical parameters included gender, age, stage, performance status, constitutional symptoms, R-IPI and NCCN-IPI risk stratification, treatment history, the dates of disease progression, relapse or death and cause of death.

Tissue samples

Original diagnostic pathology reports were examined for pathologic features including germinal center (GC) vs non-GC characterization. The biopsy materials had been processed according to the established procedures. Paraffin-embedded and formalin-fixed tissue sections were used for immunohistochemical staining. The primary antibody used for immunophenotypic analysis of the lymphomas was PDL-1 (DAKO, Glostrup, Denmark). Heat-induced epitope retrieval was performed in a microwave oven by heating the slides for 5 min at 750 W and subsequently for 15 min at 500 W in retrieval buffer (Ph 6.0). The detection system Envision (DAKO) was used. The stain was developed with 3,3'-diaminobenzidine and H₂O₂, and the slides were counterstained with haematoxylin. The immunostaining was performed in a DAKO Autostainer (DAKO) according to the instructions of the manufacturer. All DLBCL, NOS biopsy materials were then reviewed at the Hematopathology Department of Evangelismos General Hospital in Athens, Greece. All pathology reviews (conducted by hematopathologists AP and LM) confirmed the initial diagnosis according to the World Health Organization (WHO) classification [55]. The use of materials (as well as clinical information) has been approved by the Ethics Committee of the Hospital and harmonized with the Declaration of Helsinki.

Immunohistochemical analysis

All IHC-stained sections were evaluated and scored by two hematopathologists independently. Threshold values of 30% for BCL2, BCL6, CD10, and MUM1 staining were chosen reflecting routine clinical practice. MYC and Ki-67 expression was recorded using a percentage scale of positive tumour ranging from 0% to 100%. Staining intensity of PD-L1 was scored as follows: 0 (no staining or staining in <5% of the tumour cells), 1 (no data due to absence of core, non-viable tissue or technical artifact), 2 (weak positive, weak staining in 5-20% of the tumour

cells), or 3 (strong positive, moderate to strong staining in >20% of tumour cells) [56]. The numbers of PD-1 positive TILs were assessed semiquantitatively and scored as follows: 0 [no positive cells/high-power field (HPF)], 1 (fewer than 10 positive cells/HPF), 2 (10-30 positive cells/HPF), or 3 (more than 30 positive cells/HPF) [57]. For both markers we decided to consider scores 0 and 1 as negative and 2 and 3 as positive.

Statistics

Comparisons of clinical and pathological data were carried out using the Fisher's exact test and survival analysis with IBM SPSS Statistics 23 software. The Independent samples t-Test was used to compare the mean OS as well as the mean complete response (CR) duration between PD-L1 positive and PD-L1 negative patients. The Kaplan-Meier method was used to plot survival curves and log-rank test to compare survival between two groups. In order to confirm the prognostic value of the proposed risk factors, age and sex-adjusted as well as multivariate analyses were performed using Cox regression models.

Results

Patient characteristics

Table 1 summarizes patient characteristics. Five (18.5%) were diagnosed with DLBCL, NOS of the GC subtype, while 22 (81.5%) with the non-GC DLBCL subtype.

Table 1. Patient characteristics

Characteristics	n (%)
Age (years)	
median	64.5
range	27-96
male gender	13 (48)
Revised International Prognostic Index (R-IPI)	
very good	5 (19)
good	7 (26)
poor	15 (55)
National Comprehensive Cancer Network (NCCN)-IPI	
low	6 (22.2)
low-intermediate	5 (18.5)
high-intermediate	9 (33.3)
high	7 (26)
Ann-Arbor stage	
I and II	11 (41)
III and IV	16 (59)
Cell of origin, COO	
Germinal Center B-cell like (GCB)	5 (18.5)
non-GCB	22 (81.5)
Median follow-up (months)	31.5

Table 2. Pathological findings

Pathological findings	PD-1 in tumor Infiltrating Leukocytes		PD-L1 positivity			Total PD-L1 positive samples	PD-L1 negative samples	p^1	p^2	p^3
	positive	negative	in the malignant cells only	in the non-malignant cells only	in both malignant and non-malignant cells	n (%)	n (%)			
	n (%)	n (%)	n (%)	n (%)	n (%)					
Total	6 (22.2)	21 (77.8)	7 (25.9)	1 (3.7)	13 (48.1)	21 (77.8)	6 (22.2)			
Phenotype								0.303	0.056	
GCB	3 (11.1)	2 (7.4)	2 (7.4)	0 (0)	1 (3.7)	3 (11.1)	2 (7.4)			1.00
non-GCB	3 (11.1)	19 (70.4)	5 (18.5)	1 (3.7)	12 (44.4)	18 (66.6)	4 (14.8)			0.544
BCL-2								0.662	0.187	
<30%	4 (14.8)	7 (25.9)	1 (3.7)	1 (3.7)	6 (22.2)	8 (29.6)	3 (11.1)			0.576
≥30%	2 (7.4)	14 (51.8)	6 (22.2)	0 (0)	7 (25.9)	13 (48.1)	3 (11.1)			0.475
MYC								0.638	0.638	
<40%	3 (11.1)	14 (51.8)	5 (18.5)	0 (0)	9 (33.3)	14 (51.8)	3 (11.1)			0.082
≥40%	3 (11.1)	7 (25.9)	2 (7.4)	1 (3.7)	4 (14.8)	7 (25.9)	3 (11.1)			1.00
Ki-67								0.363	0.638	
<80%	3 (11.1)	7 (25.9)	2 (7.4)	0 (0)	7 (25.9)	9 (33.3)	1 (3.7)			0.183
≥80%	3 (11.1)	14 (51.8)	5 (18.5)	1 (3.7)	6 (22.2)	12 (44.4)	5 (18.5)			1.00

Fisher's exact test. p^1 : PD-L1 positive versus PD-L1 negative. p^2 : PD-1 positive versus PD-1 negative; p^3 : PD-1 expression in non-malignant cells versus PD-L1 expression in non-malignant cells. Significance threshold set at 0.05. Percentages: % of the total.

Table 3. Patient clinical characteristics

Pathological findings	PD-L1 positive samples n (%)	PD-L1 negative samples n (%)	p^1
Total	21 (77.8)	6 (22.2)	
Age group			1.00
≤60 years old	10 (37)	3 (11.1)	
>60 years old	11 (40.7)	3 (11.1)	
Gender			0.385
Male	9 (33.3)	4 (14.8)	
Female	12 (44.4)	2 (7.4)	
Constitutional symptoms			1.00
Present	13 (48.1)	2 (7.4)	
Absent	8 (29.6)	4 (14.8)	
R-IPI score			1.00
Poor	12 (44.4)	3 (11.1)	
Good/Very Good	9 (33.3)	3 (11.1)	
NCCN-IPI score			0.588
L	4 (14.8)	2 (7.4)	
L-I/H/H-I	17 (63)	4 (14.8)	
Ann-Arbor stage			1.00
I-II	9 (33.3)	2 (7.4)	
III-IV	12 (44.4)	4 (14.8)	
Tumour size			0.662
≤7.5	13 (48.1)	3 (11.1)	
>7.5	8 (29.6)	3 (11.1)	
CR to 1 st line treatment			1.00
Yes	14 (51.9)	4 (14.8)	
No	7 (25.9)	2 (7.4)	

Fisher's exact test. p^1 : PD-L1 positive versus PD-L1 negative. Significance threshold set at 0.05. Percentages: % of the total.

The pathological findings of the patients of the study are shown in Table 2. The detection of PD-1 ranged about 22%. Out of the 27 DLBCL cases, 77.8% were found to be PD-L1 positive. PD-L1 positive cases were associated with a higher rate of non-GCB phenotype as well as BCL-2 positivity, MYC negativity and more pronounced Ki-67 staining compared to PD-L1 negative cases but none of the differences appeared to be statistically significant.

Clinical outcome

All patients but one (95%) with PD-L1 positive DLBCL completed their assigned course of treatment compared to all the patients with PD-L1 negative DLBCL. No statistically significant difference was found when comparing the clinical characteristics of PD-L1 positive versus PD-L1 negative patients (Table 3).

Eleven (52.4%) PD-L1 positive DLBCL patients did not survive, in comparison to 2 (33%) PD-L1 negative patients. The main cause of death was relapsed/refractory disease. Patients with PD-L1 positive DLBCL had shorter OS and CR duration but none of the differences were statistically significant (Table 4 and Figure 2).

The mean CR duration for PD-L1 negative patients was 72.67 (CI 31.552-113.782) and 70.91 months (CI 51.243-90.58) for PD-L1 positive patients respectively, without any statistically significant difference ($p=0.832$; Figure 3A). Moreover, the log-rank test failed to reveal any difference between the PD-L1 positive and PD-L1 negative groups regarding OS (75.50 vs 80.0 months, $p=0.949$; Figure 3B).

Age- and sex-adjusted Cox regression analysis of prognostic factors regarding OS revealed that high-stage (III, IV) and a high NCCN-IPI score were unfavourable factors but with no statistical significance. In a multivariate model including the aforementioned factors, a high NCCN-IPI score remained a strongly unfavourable factor but still statistically insignificant (Table 5).

Discussion

In our study we found that PD-L1 expression is not a prognostic factor for the OS of our cohort of DLBCL, NOS patients, while the number of PD-1 positive TILs was not statistically significantly associated with PD-L1 expression.

PD-1 signalling physiologically mitigates T cell stimulation and protects adjacent tissues from

Table 4. Comparison of OS and CR duration between PD-L1 positive and PD-L1 negative patients, using independent samples t-test

	PD-L1 expression		Mean Difference (mean \pm SEM)	95% CI	p
	Positive (mean \pm SEM)	Negative (mean \pm SEM)			
CR duration (months)	28.19 \pm 6.561	41.03 \pm 16.75	8.81 \pm 15.07	-22.23, 39.85	0.564
OS (months)	35 \pm 6.453	45.50 \pm 15.66	10.50 \pm 14.60	-19.56, 40.56	0.479

SEM: Standard error of the mean; CI: Confidence interval. Significance threshold set at 0.05

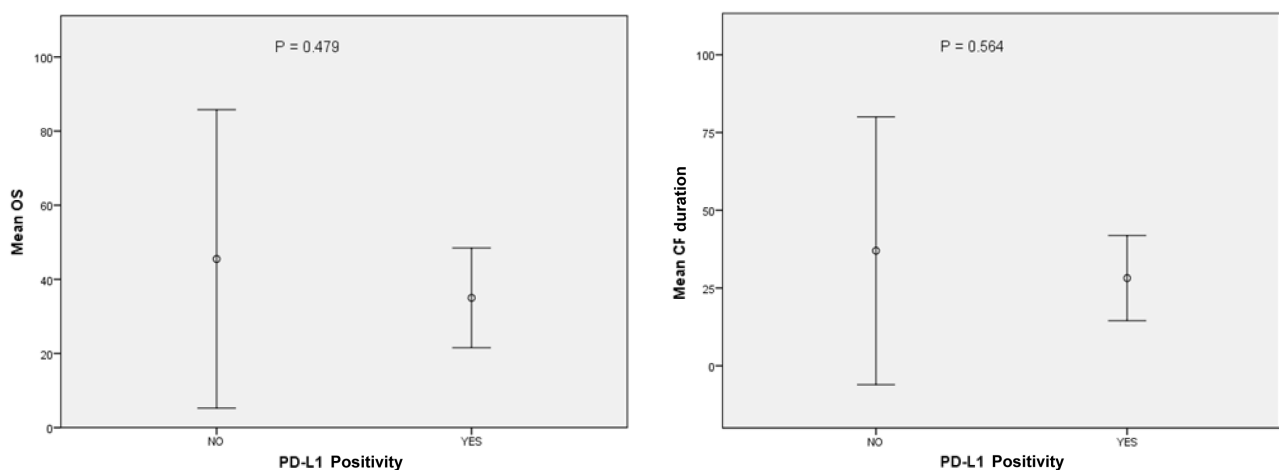


Figure 2. Mean OS and CR duration in PD-L1 positive and negative groups.

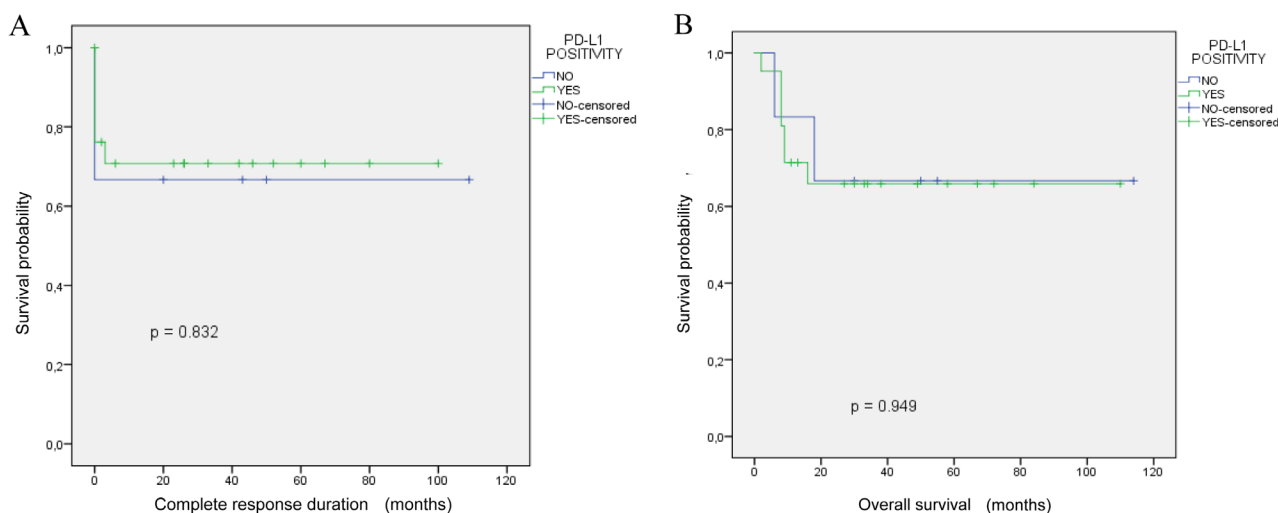


Figure 3. Survival curves.

Table 5. Prognostic factors affecting overall survival

Prognostic factors	Age- and sex-adjusted analysis		Multivariate analysis [#]	
	HR (95% CI)	p	HR (95% CI)	p
PD-L1 positive vs. PD-L1 negative	0.872 (0.168-4.515)	0.871	0.461 (0.069-3.070)	0.423
Non-GCB vs. GCB	0.452 (0.055-3.715)	0.452	0.223 (0.020-2.752)	0.248
Stage III-IV vs. I-II	2.205 (0.388-12.532)	0.372	0.263 (0.006-11.179)	0.485
Constitutional symptoms vs. no constitutional symptoms	1.006 (0.256-3.948)	0.994	0.494 (0.105-2.328)	0.373
R-IPI poor vs. good-very good	0.212 (0.021-2.113)	0.186	0.034 (0.002-4.076)	0.167
NCCN-IPI low-intermediate, high-intermediate, high vs. low	1.402 (0.141-13.913)	0.773	2.982 (0.165-53.752)	0.459

Significance threshold set at 0.05. HR: Hazard Ratio, CI: Confidence interval. #: The variables included in the multivariate analysis for OS were age, sex, PD-L1 expression, cell of origin, stage, presence of constitutional symptoms, R-IPI and NCCN-IPI scores.

inflammation expansion, providing a balance between effective immune response and immune-induced tissue damage. On the contrary, its role in case of certain malignancies is harmful as it contributes to immune evasion of neoplastic cells [38,58-61]. PD-1 and PD-L1 have been detected in various hematologic malignancies [7,62-76]. The diagnostic and prognostic value of PD-1 positive TILs has been previously demonstrated in various malignancies of the lymphatic tissue [64,68,69,77,78]. In fact, in one study the decrease in PD-1 expression was associated with clinical improvement [73]. PD-L1 has been detected primarily in biopsies of Primary Mediastinal B-cell lymphoma (PMBCL) patients but also in non-GC subtype DLBCL patients [5,71,74,78-81]. PD-L1 expression is much less pronounced on neoplastic cells than non-neoplastic cells, mainly macrophages, and its detection appears to affect the prognosis of patients [78-87], although not all studies suggest so [57]. These different results are probably due to different patients' populations among studies, different PD-L1 reagents or even a more complex biology of

the microenvironment and interactions between different molecules and cells involved in the pathogenesis of this heterogeneous disease.

PD-1 has been similarly detected on both lymphoma cells and TILs in as many as 40-60% of patients with DLBCL [88] and the increased presence of PD-1 positive TILs has been associated mainly with a better OS rate [6,57,72,79,86], while contradictory results have been described in a more recent study [88] with the latter being similar to what is seen in patients with solid tumours [53,54]. Finally, in patients with DLBCL it has been found that the presence of helper CD4 positive T lymphocytes is suppressed by the presence of T regulatory cells and PD-1 / PD-L1 interaction [65].

It is worth mentioning that the genetic basis of lymphoma cells' immune escape through PD-1 / PD-L1 pathway is not fully established. For the time being, increased expression of PD-L1 has been associated with its gene amplification and transduction of an ectopic promoter [71,74,80,82]. Recently additional mechanisms have been described which include either structural altera-

tions of PD-L1 gene or increased B- cell receptor (BCR) activation and further transmission of the intracellular signal via Myc or NFkappaB pathway [89,90].

It appears that immunohistochemical detection of immune receptors and their ligands in DLBCL, NOS is in dire need of improvement in order to be considered objective or even reliable. In the study by Laurent et al and in others a very high PD-L1 positivity was found [7,57,91], while other authors have reported a PD-L1 positivity rate of only 11-15% [82,85]. The positivity threshold for PD-L1 has been 30% in most of the studies [78,81,82,85,92], while in other studies lower cut-off values such as 5% of all cells have been used, or even it has been sufficient that the majority of cancer cells express PD-L1 [5,74,93] or finally there has been no limit regarding positivity [94]. One obvious reason for the existence of numerous suggestions for a cut-off value of positive PD-L1 staining is the subjectivity of the estimation of the positivity of an immunohistochemical staining. This difficulty of objectively assessing the PD-L1 positivity could be mitigated by using dual dye techniques, such as the one for PD-L1 and PAX5 proteins [5,7,82,85]. PD-L1 positive DLBCL, NOS is mainly associated with the non-GC histological subtype [5,7,74,82,85,95], an observation made in our study as well. This particular subtype is characterized by a worse prognosis than GC subtype. Thus, it appears that while PD-L1 expression among BNHLs is unusual, it mainly involves the non-GC histological subtype whose gene expression analog (Activated B-cell, ABC lymphoma) has markedly worse prognosis than the molecularly defined GCB subtype [96-98]. It is therefore possible that PD-L1 expression contributes to this difference in survival between patients with GCB and ABC DLBCL, which remains to be elucidated in genomic expression studies.

Our study has certain advantages, such as the central review of specimens and the homogeneous treatment and follow-up that patients with DLBCL, NOS have received. Some disadvantages of our study need also to be mentioned. First of all, the small sample of patients results in increased variability and dictates the need to confirm the results in a larger population. Second, our study was retrospective, so a prospective study is needed. Third, the median follow-up of our patients has been rather short so far, however event-free survival at 24 months has a strong correlation with OS in *de novo* DLBCL, so this follow-up may in fact be sufficient to determine outcomes [99]. Finally, detection of PD-1 and PD-L1 was done only by immunohistochemical methods, so additional gene

and transcriptional studies are needed to fully investigate the biological significance of their expression among patients with DLBCL, NOS.

In summary, expression of PD-L1 in DLBCL neoplastic cells may lead to more aggressive biological behaviors, and inhibition of the PD-1 / PD-L1 pathway with monoclonal antibodies could have a therapeutic role in some patients. In fact, it has been found from previous studies that the administration of PD-1 monoclonal antibodies, pidilizumab and nivolumab, is effective in patients with DLBCL [100,101]. Contrary to that, the findings of our study do not support the idea that PD-L1 expression can affect the prognosis, however immunological targeting of the PD-1 / PD-L1 axis could be exploited to benefit a subgroup of DLBCL, NOS patients, perhaps depending on the degree of PD-L1 expression as it seems to be the case in solid tumours [102,103]. Such a therapeutic approach has inherent advantages, such as modification of the function of immune cells mostly at a local level (e.g., in cancerous tissue), alleviation of immune deficits due to neoplastic cells and synchronous restoration of the function of the already stimulated immune cells [104]. A clear identification however of patients who will benefit most from targeted immunomodulatory treatments (as well as those most likely to experience severe side effects), the most appropriate time and route of administration and its duration, and assessment of response to treatment should be a priority, as it has already been attempted for example with the immune-related response criteria (irRC) [105,106].

Of great interest is also the possible combination of cytotoxic therapies with inhibitors of immune receptors. The proinflammatory activity and release of immunogenic molecules in the malignant tumour region following chemotherapy administration may increase the antitumour activity of the above therapies at a rate proportional to the rate of proliferation of the cancer cells, since the faster they divide the more vulnerable they are to chemotherapy. On the other hand, it has been shown that the above combinations lead to lymphopenia, with the potential to impair the action of PD-1 / PD-L1 axis inhibitors which relies significantly on the activity of effector T cells. Similarly to newly developed immunotherapies, conventional (fractionated) radiotherapy has seemingly contradictory effects by increasing the expression of PD-L1 in lymphoma cells and of PD-1 in CD8 positive T lymphocytes as well as leading to the destruction of TILs that appear on the affected tissue 7 days after the onset of radiotherapy [107]. The biggest challenge however in the near future will be to find the best possible combination of therapies that

target the various cancer / lymphoma cell immune evasion mechanisms. This discovery will pave the way for completely individualized therapies for lymphoma patients, either by assigning them to a combination of chemotherapy and a PD-1 / PD-L1 antagonist, or by completely reconstructing a sufficient immune antitumour mechanism exclusively via combination of immunological therapies such as immune receptor inhibitors, monoclonal anti-

bodies, costimulatory molecules, Bispecific T-cell Engagers (BiTEs) and Chimeric Antigen Receptors (CAR) T cells, or via combination with other non-chemotherapeutic approaches such as micromolar inhibitors [108-111].

Conflict of interests

The authors declare no conflict of interests.

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