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Primary mediastinal large B-cell lymphoma

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ABSTRACT

Primary mediastinal large B-cell lymphoma (PMLBCL) is a distinct clinical and biological disease from other types of DLBCL. It is more frequent in young female and constitutes 6%-10% of all DLBCL. PMLBCL is characterized by a diffuse proliferation of medium to large B-cells associated with sclerosis. Molecular analysis shows it to be a distinct entity from other DLBCL. Rituximab CHOP/MACOP-B-like regimens followed by mediastinal radiotherapy (RT) were associated with a 5-years PFS of 75%–85%. More intensive regimens, as DA-EPOCH-R without mediastinal RT, have shown very promising results, but this therapeutic advance needs to be confirmed in further prospective trials. The

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role of consolidative mediastinal RT should be still better assess in prospective comparative studies. PET-CT scan is a powerful tool to define the real quality of response and it is hoped that future prospective trials may allow its role in the de-escalation of mediastinal RT.

1. General information

1.1. Definition

Primary mediastinal large B-cell lymphoma (PMLBCL) is an uncommon, but not rare, clinicopathological entity. It has a worldwide distribution, and is listed as a separate entity in the updated WHO classification of Lymphoid Malignancies (Swerdlow et al., 2016). It occurs more often in young females, and originates in the mediastinum, where it frequently presents with features of local invasion. The term "primary mediastinal large B-cell lymphoma" is now accepted as a definition of a unique type of B-cell lymphoma that was previously classified with lymphomas of cleaved and non-cleaved germinal centre cells or immunoblastic lymphoma under the Kiel and Working Formulation classifications (Lennert, 1978). Primary mediastinal large cell lymphoma has been postulated as arising from a putative thymic medulla B cell (Addis and Isaacson, 1986; Hofmann et al., 1988).

1.2. Incidence

Primary mediastinal large B-cell lymphoma is an uncommon tumour that occurs throughout the world (Bunin et al., 1986; Jacobson et al., 1988; Perrone et al., 1986; Waldron et al., 1985). It constitutes 2–3% of all NHL (NHL classification project) and 6%–10% of all Diffuse Large Cell Lymphoma (Cazals-Hatem et al., 1996; Falini et al., 1995).

Only one large population based study was able to estimate incidence of PMLBCL. Incidence was calculated in the US population using data from the SEER database (Liu et al., 2016). Based on slightly more than 400 patients diagnosed between 2000 and 2012, the annual incidence rate was 0.4 per million. Female had significantly higher incidence than males (ratio 3:1). However, this difference was apparent for the white population only. A peak of incidence was shown at 30–39 years for white, black, and other groups. Between 2001 and 2012 there was a trend towards increasing incidence rate in all ages, all races, and both sexes. The phenomenon can be partially explained by the increase recognition for this subtype of lymphoma.

1.3. Survival

Five-year survival was 85% with no difference between whites and blacks. Prognosis reduced with advancing age: 5-year survival was significantly lower for patients aged 60 and more. The adjusted risk ratio from a multivariate analysis estimated a 3.5 higher risk of the elderly (>60 years) compared with the young adults (18–39 years). From this population based study, other significant prognostic variables were: socioeconomic status, "others populations" group, and stage. The late stage (III/IV) had an 80% higher risk compared to early stage patients (I/II). The same percentage of risk was found in the comparison between other population and whites. Socioeconomic status (medium poverty *vs.* low poverty) had almost a double risk of dying (Liu et al., 2016).

1.4. Risk factors

The study reported by Liu (Liu et al., 2016) revealed a trend of increasing disease incidence rates in all racial and gender subgroups during 2001–2012. This increase may be partially attributed to higher risks of exposure to factors associated with lymphomagenesis, although the exact causes for this increase are still unclear. The same study revealed an incidence peak at 30–39 years for whites, blacks, and other groups. Notably, black women and men showed a similar incidence rate, whereas in whites the PMLBCL incidences were significantly higher in women. Many factors such as genetic susceptibility, environmental risk, dietary factors, occupational exposures, autoimmune diseases, infectious conditions, and socioeconomic status are known to affect cancer incidences (Koshiol et al., 2011; Smedby and Hjalgrim, 2011) and may contribute to the increased occurrence in different populations. Up to now the reasons for complex demographics of PMLBCL observed in different ethnic groups currently remain unclear. Therefore, more advanced study in this area, especially investigation of the roles of genetic factors, gender factors, and gene-environment interactions in affecting development of this disease is needed.

No particular risk factors have been clearly identified for PMLBCL.

2. Pathology and biology

2.1. Morphology

Primary mediastinal B-cell lymphoma (PMBL) is characterized by a diffuse proliferation of medium to large B-cells associated with sclerosis and a degree of compartmentalisation (Harris et al., 1994). Lymphomatous elements show polymorphic nuclei and a wide rim of cytoplasm that is either clear or slightly basophilic. The fibrotic reaction is easily appreciated in the form of thin strands of reticulin fibres that surround clusters of neoplastic cells. In more than half of cases, there are prominent collagen bands that emphasise the compartmentalisation. Such features may lead to a misdiagnosis of germ cell tumour or even clear-cell thymoma. Focal nodularity, extensive necrosis, vascular invasion, thymic remnants, and scattered multinucleated giant cells, occasionally with Reed-Sternberg-like features, can sometimes be seen (Jaffe et al., 2001; Harris et al., 1994; Pileri et al., 2003). In this regard, it should also be noted that "grey zone" borderline cases combining features of PMBCL and cHL or cases of composite PMBCL and cHL can rarely be encountered (Traverse-Glehen et al., 2005).

2.2. Immunophenotype

Regarding immunohistochemical analysis, despite generally lacking surface and cytoplasmic immunoglobulin (Ig), PMBCL expresses B-cell-related antigens such as CD19, CD20, CD22, CD79a, PAX5 and CD45. CD30 staining is observed in the vast majority of cases (~80%), although it is weaker and less homogeneous than in cHL and ALCL. CD15 is occasionally present. Tumour cells are more frequently positive for BCL2 (55–80%), CD23 (70%), while BCL6 expression is variable (45–100%) and CD10 is more often negative (8–32%). MAL protein positivity is recorded in about 70% of cases, a finding that differs from the occasional occurrence in diffuse large

Table 1
Pathological and immunophenotypic comparison of primary mediastinal large B cell lymphoma (PMBCL); nodular sclerosis classical Hodgkin lymphoma (cHD); mediastinal grey zone lymphoma (MGZL); diffuse large B cell lymphoma (DLBCL).

Features	PMBCL	cHL	MGZL	DLBCL
Morphology	Sheets of large cells; clear cells; no inflammatory	Lacunar Hodgkin Reed-Sternberg cells; Inflammatory polymorphous infiltrate	Sheets of pleomorphic large cells; Lacunar Hodgkin Reed Stenberg cells; sparse inflammatory infiltrate	Sheets of large cells with variable aspects
Sclerosis	70%-100% (alveolar, fine bands)	100% (large bands)	Focal fibrous bands	Absent
CD45	Positive	Negative	Positive	Positive
CD30	Positive weak (70%-80%)	Positive	Positive	Rare (anaplastic variant)
CD15	Negative	Positive	Positive	Negative
CD20	Positive	Negative	Positive	Positive
CD23	Positive	Negative	Negative	Negative
CD79a	Positive	Usually negative	Positive	Positive
PAX-5	Positive	Weak positive	Positive frequently	Positive
Immunoglobulin	Negative	Negative	Negative	Positive
BOB-1	Positive	Negative	Positive frequently	Positive
OCT-2	Positive	Negative	Positive frequently	Positive
MAL expression	60%–70%	<20%	30%–40%	<10%

B-cell lymphoma (DLBCL) and classical Hodgkin lymphoma (cHL) (Copie-Bergman et al., 2002). This molecule is located in detergent-insoluble glycolipid-enriched membrane (GEM) domains that are involved in lipid-raft mediated membrane trafficking and lymphocyte signal transduction: its abnormal expression might have significant implications in PMBL lymphomagenesis and neoplastic growth control. Immunohistochemical determination of FIG-1 is in line with the recent observation of Copie-Bergman et al., who have reported high FIG1mRNA levels in PMBL but not in non-mediastinal DLBCL. The authors postulated that FIG1 expression may be due to activation of a cytokine signalling pathway in PMBL and, as such, may represent a potential molecular marker (Copie-Bergman et al., 2002). The co-expression of BCL-6 and MUM1/IRF4 in PMBL suggests deregulated transcription of these proteins and strengthens the idea of possible derivation from cells that have already passed through the germinal centre reaction (Klein et al., 2003).

2.3. Differential diagnosis

The main differential diagnoses are cHL and DLBCL. Classical Hodgkin lymphoma can be distinguished from PMBCL by histological features such as abundant infiltration with granulocytes and lymphocytes as well as histiocytes in the former. In addition, cHL expresses CD15 and less often a full set of B-cell markers. MAL has been reported to be specifically expressed in PMBCL, but is rather a difficult marker to stain for in routine practice. Some cases with either morphological features of PMBCL but immunophenotypical features of cHL or vice versa do not allow a final diagnosis and are classified as B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL or so-called mediastinal grey zone lymphoma (MGZL). These tumours on morphology showed cells larger and more pleomorphic than in the typical cases of PMBCL. Pleomorphic cells resembling lacunar cells and HL cells. A typical characteristic feature is the broad spectrum with different areas of the tumour some more closely to cHL and others appear more like DLBCL. On immunophenotype analysis neoplastic cells typically express CD45 but in contrast with cHL the B-cell programme is often preserved, but it is aberrantly expressed in concert with cHL markers, such as CD30 and CD15. CD20 and CD79a are also frequently positive and may be strongly expressed on the majority of tumour cells. The transcription factors PAX-5, OCT2 and BOB1 are also usually expressed (Table 1).

The differential diagnosis with nodal DLBCL- NOS is not always easy. The distinct morphological features of PMBCL, such as clear cell proliferation and sclerosis, may be difficult to evaluate on small biopsies and there is a lack of well-defined diagnostic criteria that can be routinely applied. The expression of CD23 in PMBCL may be useful in that respect. Gene expression analysis allows for an improved distinction between PMBCL and DLBCL-NOS but can as yet not be used in clinical practice.

2.4. Molecular characteristics

PMBCL has a unique Gene Expression Profile (GEP) transcriptional signature different from other nodal DLBCL and closer to typical cHL signature, characterized by constitutively activated JAK2 and frequent amplification of PDL1 and PDL2. The underlying genetic basis for these observations is the recurrent amplification involving JAK2 on chromosome band 9p24 seen in 50–70% of PMBL. JAK-STAT pathway deregulation is the hallmark of PMBCL and positively regulates the expression of PDL1 and PDL2. This translocations involving CIITA, a transactivator of MHC class II genes, occur in ∼40% of PMBCL and represent a second mechanism of immune escape of this lymphoma. CIITA translocations invariably fuse the N terminus of CIITA in frame with a variety of other genes. As a result, one copy of CIITA is inactivated, and the fusion protein can also act in a dominant-negative manner to extinguish MHC class II expression, thereby limiting the ability of the tumour cells to interact with T cells. PDL1 and PDL2 overexpression and MHC-II downmodulation are instrumental in PMBCL to survive in the thymic microenviroment. This may ultimately contribute to immune escape of the tumour cells (Twa et al., 2014). A gain at 2p16 region leads to duplication of REL proto-oncogene that encodes a transcription factor of the nuclear factor kappaB (NFKB) family (Nedomova et al., 2013). These features confirm a molecular similarity between PMBCL and HL and support that constitutive activity of NFKB and JAK-STAT pathways can be taken as molecular hallmark of PMBCL. JAK-STAT positively regulate the expression of PDL1 and PDL2. These studies could be considered as preclinical model for a targeted therapy of PMBCL demonstrating that the blockade of NFKB, and JAK-STAT pathway as well as PD/PDL1 antibody could be potential therapeutic strategies (Rossi et al., 2005; Steidl and Gascoyne, 2011).

3. Diagnosis

3.1. Clinical presentations

PMBCL normally presents with a bulky tumour in the anterior mediastinum that is rapidly progressive and gives rise to local compressive symptoms including early dyspnoea, cough, dysphagia and compromising the airway or great vessels, producing a superior vena cava syndrome. Up to one half of patients have symptoms and signs of superior vena cava syndrome, thoracic and neck vein distension, facial oedema, conjunctival swelling, and occasionally arm oedema. This results in relatively early presentation so that at diagnosis, most patients (around 80%) have stage I or II disease (Jacobson et al., 1988; Levitt et al., 1982; Brugger et al., 1994). The mediastinal tumour is frequently bulky, being over 10 cm in about 70–80% of patients infiltrating the lung, chest wall, pleura, and pericardium. Pleural or pericardial effusions are present in one-third of cases (Lazzarino et al., 1997; Zinzani et al., 1996). Breast oedema is common and hoarseness may reflect recurrent laryngeal nerve damage. Despite the local invasiveness, distant spread is infrequent at the onset, and even spread to the supraclavicular nodes is not unusual at presentation. Extranodal sites may, however, be involved, particularly in cases of disease recurrence, with a propensity for involvement of the kidneys, adrenal glands, liver, and ovaries and central nervous system (CNS) (Lazzarino et al., 1997; Zinzani et al., 1996; Haioun et al., 1989; Kirn et al., 1993; Lazzarino et al., 1993; Todeschini et al., 1990). The duration of symptoms is rarely longer than 3 months. Systemic symptoms, mainly fever or weight loss, are present in less than 20% of cases. Spread to marrow or cerebrospinal fluid involvement is unusual. Moderate to high LDH levels are observed in 70%–80% of cases. Any recurrence is almost always seen in the first two years of follow-up (Jacobson et al., 1988; Todeschini et al., 1990). Mediastinal gray zone lymphoma (MGZL) shows similar clinical features, but compared to PMBCL is more common in young men, more often presents extranodal involvement and B symptoms (Table 2).

3.2. Diagnostic criteria

The diagnosis PMLBCL is made on clinical, morphological, and immunophenotypic, criteria. Key features are a large anterior mediastinal mass and histology showing the presence of large B-cells with variable nuclear features, resembling centroblasts, large centrocytes or multilobated cells, often with pale cytoplasm. The tumour cells are entwined and encircled by strands of fibres (Lennert, 1978). Sclerosis is marked in approximately half the cases, and may constitute a dominant feature of the microscopic picture (Lamarre et al., 1989; Lavabre-Bertrand et al., 1992; Perez-Soler et al., 1984; Paulli et al., 1997). In some series, sclerosis has been defined as a diagnostic criterion, but its variability in different areas of the same tumour makes this an impractical diagnostic requirement with the small biopsy samples usually available. Remnants of fibrous tissue reminiscent of thymus are detected in one third to one half of specimens (Perrone et al., 1986; al-Sharabati et al., 1991). Stains for keratin and cytokeratin may highlight residual thymic epithelial cells. Diagnostic tissue samples may be obtained by mediastinoscopy, by percutaneous needle biopsy of the tumour mass through the chest wall, or by anterior mediastinotomy or minithoracotomy. Formal thoracotomy is rarely required and total excision neither feasible nor necessary (Elia et al., 1992). In patients with airway compromise caused by tumour compression it is safer to carry out a percutaneous procedure with local anaesthesia than to risk a general anaesthetic for a more extensive biopsy such as difficult extubation following the procedure because of airway compromise. No reliable molecular markers are available for monitoring of minimal residual disease in PMLBCL.

Table 2
Clinical charateristics comparison of primary mediastinal large B-cell lymphoma (PMBCL); diffuse large B cell lymphoma (DLBCL); nodular sclerosis classical Hodgkin lymphoma (NScHD); mediastinal gray zone lymphoma (MGZL).

Features	PMBCL	cHL	MGZL	DLBCL
Female/male ratio	3:1	1:1	1:2	1:1
Median age	35	28	35	55
Stage I-II	70%–80%	55%	70%–80%	30%
Mediastinal invol.	All	80%	80%	20%
Extra-nodal sites	Uncommon	Uncommon	Uncommon	Common
Bone marrow	2%	3%	3%	10%–15%
Elevated LDH	70%–80%	Rare	70%–80%	50%
B symptoms	<20%	40%	40%	50%
Bulky disease	70%–80%	50%	70%–80%	10%–15%

4. Staging

4.1. Staging procedures

Complete staging work-up for PMLBCL is the same as that used routinely for nodal NHL. It includes an accurate physical examination, complete haematological and biochemical exams, total-body computerized tomography, and bone marrow aspirate and biopsy. MRI may have a role for the definition of the intrathoracic extension of disease, but remains abnormal or difficult to interpret in residual masses (Abrahamsen et al., 1994). PMBCL shows almost universal avidity for [18F]-2-fluoro-2-deoxyglucose, making positron emission tomography (FDG-PET) an effective means to assess disease extent and to characterize residual masses at the completion of treatment. The extent of experience with this technique is however too limited to permit major changes to therapy based upon FDG-PET scans at present, pending the results of prospective trials. The standard staging system used for diffuse large B-cell lymphomas is the same as that proposed for Hodgkin's disease at the Ann Arbor Conference in 1971 (Carbone et al., 1971).

4.2. Restaging procedures

Restaging should include all the diagnostic procedures which were positive at time of diagnosis and initial staging. With this type of lymphoma the presence of a small residual mass within the anterior mediastinum is almost invariable at the completion of therapy, and this is a frequent cause of uncertainty for management. Several recent studies have suggested that 18FDG PET may be an exceptionally useful tool for evaluation of residual masses considering the elevated tracer uptake that characterizes active lymphoma (Knopp et al., 1994; Jerusalem et al., 1999; Spaepen et al., 2002; Zinzani et al., 2004).

However, false positives due to elevated 18FDG uptake in thymic hyperplasia in young patients and inflammation could represent major limitations for PET-guided response assessment (Smith et al., 2007). Moreover, the role of PET scan in the follow-up of mediastinal lymphomas should be better defined, due to its recently reported lack of discrimination (Zinzani et al., 2007). Histological confirmation of lymphoma relapse appears mandatory; it can safely be carried out with various biopsy techniques, the choice of which should be made on the basis of the findings of the clinical and imaging studies of the individual case (Zinzani et al., 2007).

Table 3
Pre-Rituximab based chemotherapy studies for primary mediastinal large B cell lymphoma (PMBCL).

Reference	No. Pts	Regimen	CR rate (%)	RFS (%)	OS (%)
Todeschini et al. (1990)	21	CHOP (6)	0	90 (5 yrs)	nr
		MACOP-B (15)	87		
Lazzarino et al. (1993)	30	CHOP	36	72 (3 yrs)	36 (3 yrs)
		MACOP-B	73		
Cazals-Hatem et al. (1996)	141	M-BACOD	79	61 (3 yrs)	66 (3 yrs)
		ACVBP			
Lazzarino et al. (1997)	106	CHOP (47)	37	71 (3 yrs)	52 (3 yrs)
		V/MACOP-B (62)	58		
Martelli et al. (1998)	37	MACOP-B + IFRT (27)	88	91 (5 yrs)	93 (5 yrs)
		F-MACHOP + IFRT (10)	60	60 (5 yrs)	70 (5 yrs)
Zinzani et al. (1999)	50	MACOP-B + IFRT	86	93 (5 yrs)	73 (3 yrs)
Zinzani et al. (2001)	89	MACOP-B + IFRT	88	91 (5 yrs)	34 (3 yrs)
Todeschini et al. (2004)	138	CHOP +/− IFRT (43)	51	39 (5 yrs)	nr
		V/MACOP-B +/− IFRT (95)	80	76 (5 yrs)	nr
Zinzani et al. (2002)	426	CHOP +/− IFRT (105)	61	33 (10 yrs)	44 (10 yrs)
		V/MACOP-B +/− IFRT (277)	79	67 (10 yrs)	71 (10 yrs)
		HDS-ASCT (44)	75	78 (10 yrs)	77 (10 yrs)
De Sanctis et al. (2008)	92	MACOP-B + IFRT	87	81 (5 yrs)	82 (5 yrs)
Mazzarotto et al. (2007)	53	V/MACOP-B + IFRT	42	87 (5 yrs)	94 (5 yrs)

5. Prognosis

5.1. Prognostic factors

The utility of the International Prognostic Index (IPI) in PMBCL is limited by the age distribution of the disease and its usual confinement to the mediastinum. This is reflected in the observation that half of patients have low IPI scores at presentation. The age-adjusted IPI has similarly been reported to be of limited predictive value in PMBCL. This may reflect differences between studies, assigning patients as either stage IV or stage IIE when contiguous extranodal sites such as the lung are involved. Elevated LDH to more than twice the upper limit of normal, age over 40 and performance status ≥2 correlated with reduced survival in a population-based series from British Columbia while in a large series from the International Extranodal Lymphoma Study Group (IELSG), male sex, poor performance status and advanced-stage disease were significant negative predictors. The presence of non contiguous mediastinal extranodal disease (kidneys, adrenal glands, liver, and ovaries) at diagnosis and/or early inadequate response to induction therapy, considered as a response less than PR, should be considered significant prognostic factors for a poor outcome.

6. Treatment

6.1. Front line therapy

The first line treatment and its outcome is critical in managing PMBCL. Salvage treatment for recurrence/progression of disease is of limited efficacy. On the basis of this concept, the imperative is to cure with the first-line treatment. The first issue to consider is represented by the choice of initial chemotherapy first-generation versus third-generation chemotherapy regimens and, the inclusion of Rituximab in the front-line treatment. Other issues include any potential benefit from high-dose therapy in first remission, the role of consolidation radiotherapy to the mediastinum and the potential role of functional imaging (FDG-PET) to guide treatment choices. It is however important to strike an appropriate balance between delivery of the highest possible cure fraction and minimising the long-term morbidity for this young population of patients.

6.2. Chemotherapy regimens in pre-Rituximab era

Early studies suggesting that PMBCL were unusually aggressive, with a poorer prognosis with respect to other nodal diffuse large cell lymphomas, have been contradicted by more recent reports. Prior to the introduction of Rituximab some retrospective and prospective series suggested that a superior outcome in PMBCL might be achieved with more intensive third generation regimens. Whereas the CHOP regimen has been used by American investigators (Kirn et al., 1993; Abou-Elella et al., 1999; Lichtenstein et al., 1980; Rodriguez et al., 1994), several European centres have suggested that the V/MACOP-B (etoposide/methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin) regimen may be superior to CHOP (Lazzarino et al., 1993; Todeschini et al., 1990; Martelli et al., 1998; Zinzani et al., 1999; Zinzani et al., 2001; Zinzani et al., 2002; Todeschini et al., 2004). However, the debate is still open because it is difficult to compare the advantages of the different types of protocols, and it is also difficult to explain the rather different CR and survival rates reported by different institutions using similar regimens in phase 2 studies. In addition, two large multicentric retrospective studies have reported data regarding the comparison between CHOP and CHOP-like regimens versus MACOP-B and MACOP-B-like regimens as induction chemotherapy in patients with PMBCL.

Todeschini et al. (Todeschini et al., 2004) reported the long-term results from a retrospective multicentre Italian experience in 138 patients with PMBCL treated with CHOP (43 patients) or MACOP-B/VACOP-B (95 patients). CR was 51% in the CHOP group and 80% in MACOP-B/VACOP-B. The addition of radiation therapy on mediastinum mass consolidation improved the outcome regardless of the type of chemotherapy.

The second study (Zinzani et al., 2002) is largest series of our multinational retrospective study from the IELSG, which reviewed the outcomes of 426 previously untreated patients with PMBCL after first-generation (CHOP and CHOP-like regimens; 105 patients), third-generation (MACOP-B,VACOP-B; 277 patients), and high-dose chemotherapy schedules (high-dose sequential and autologous bone marrow transplantation; 44 patients). In all these groups, for the most part patients underwent radiation therapy after chemotherapy. Although the complete response rate was similar between the third generation subgroup and those treated with conventional CHOP/CHOP-like regimens, the relapse rate at 3 years was significantly lower in the third generation group (12% *vs.* 23%; p = 0.02) and the projected 10 years OS and PFS were respectively

71% *vs.* 44% (p = 0.0001) and 67% *vs.* 34% (p = 0.0003). These two retrospective studies suggested the superiority of the third-generation chemotherapy strategies over first-generation ones. In addition, they highlighted the role of radiation therapy (RT) for converting from PR to CR (Table 3).

6.3. Chemotherapy regimens in the post-Rituximab era

The addition of the monoclonal antibody Rituximab to chemotherapy for DLBCL has been shown to significantly improve the CR and survival rates for both early and advanced disease (Coiffier et al., 2010; Sehn et al., 2005; Pfreundschuh et al., 2011). It seems highly likely that a similar effect will be seen in PML-BCL, which may abrogate the differences between the various chemotherapy regimens described above. The British Columbia Cancer Agency (BCCA) carried out a population-based retrospective analysis of 153 patients with PMBCL whose treatment was determined by era-specific guidelines. Between 1980 and 1992 MACOP-B or VACOP-B was used, switching to CHOP between 1992 and 2001 and then to an addition of Rituximab to CHOP (R-CHOP) thereafter. The 5-yrs OS for the entire cohort was 75%, with an 5-years OS being 87% for those treated with MACOP-B/VACOP-B, significantly higher than the 71% for those patients treated with CHOP (p = 0.048). In the multivariate analysis for OS the type of chemotherapy regimen showed a trend towards improved outcomes but this was not statistically significant. However in those patients receiving R-CHOP this difference disappeared. It is generally accepted that the addition of Rituximab to chemotherapy for PMBCL yields superior results.

The MabThera International Trial (MiNT) study compared the outcomes for 824 patients with age-adjusted IPI score of 0–1 low risk in stage II–IV or I with bulky disease DLBCL were randomized to receive CHOP or CHOP-like chemotherapy with or without rituximab, which included a subset of 87 patients with PMBCL. Patients treated with R-CHOP/CHOP like regimen resulted in a greater complete response (84% *vs.* 54%; p = 0.015), lower early progression (2.5% *vs.* 24% p <0.001), improved 3years EFS (78% *vs.* 52%; p = 0.012) and similar OS (89% *vs.* 78%; p = 0.158). Of 61 patients who received mediastinal RT because bulky or extranodal disease 30% achieved an improvement in response.

In an Italian retrospective analysis 45 previously untreated patients with PMBCL were treated with a combination of a third-generation chemotherapy regimen V/MACOP-B concurrent with rituximab and mediastinal RT. The projected 5-years OS and relapse disease free (RFS) were 80% and 88% respectively. In comparison with historical data of V/MACOP-B without Rituximab we did not find any significant difference (Zinzani et al., 2009). In a small series from Israel, the addition of Rituximab appeared to improve PFS, particularly in those patients receiving CHOP, whilst there was no difference in outcomes in a comparison between either a third generation regimen with rituximab (R- M/VACOP-B) or R-CHOP (84% and 74%, respectively; p = 0.44) (Avigdor et al., 2014). However, unlike the results of MinT study, a recent retrospective study of 63 PMBCL patients (Soumerai et al., 2014) showed a high primary induction failure of 21% with R-CHOP probably due the particular poor prognosis features of these series of patients. Overall, it appears likely that the use of Rituximab removes the distinction between different chemotherapy regimens and R-CHOP is now the most widely used for PMBCL, as it is for other types of DLBCL. More recently in a single group phase 2 study of National Cancer Institute (NCI), the addition of Rituximab to infusional dose-adjusted etoposide, doxorubicin, and cyclophosphamide with vincristine, prednisone, (DA-EPOCH-R) without radiotherapy in 51 patients with untreated PMBCL has showed a very favourable outcome with a CR in 48/51 (94%) and a 3-years EFS and OS of 93% and 97% respectively. Only three patients had evidence of disease after DA-EPOCH-R treatment; two had persistent focal disease, as detected on FDG-PET-CT, and one had disease progression. Two of these patients underwent mediastinal consolidation radiotherapy, and one was observed after excisional biopsy. These results were also confirmed in a retrospective Stanford cohort where 16 patients with PMBCL treated with DA-EPOCH-R were 100% alive and event-free over a median follow-up of 37 months (Dunleavy et al., 2013). Finally, a paediatric study (median age 16 years) demonstrated an OS of 62% in 15 patients treated with DA-EPOCH-R (Woessmann et al., 2013). These excellent results confirm the value of DA-EPOCH-R without use of RT in a small and selected series of patients accrued in single institutions and for these reasons need of a validation in a larger multicentric trial (Table 4).

6.4. Role of mediastinal consolidative radiotherapy

Consolidative mediastinal RT may improve response rate and long-term outcome in PMBCL However it is not attractive to administer radiation extensively to a group dominated by younger subjects, who may be put at increased risk of second malignancies, especially breast cancer and accelerated coronary artery disease. On the other hand, the chances of cure following recurrence of PMBCL are relatively poor, so that any approach which puts patients at increased risk of relapse is to be strenuously avoided. The best outcomes historically have been reported with regimens that incorporated radiotherapy as part of the primary treatment. It is clear from the IELSG series that many patients completing chemotherapy in PR may be converted to CR following radiotherapy and that radiotherapy may render inactive residual mediastinal masses 67gallium or PET-CT positive resulting in a long-term remission. Mazzarotto et al. (Mazzarotto et al., 2007) report that following induction chemotherapy 42% of patients were in CR, rising to 95% following radiotherapy. Univariate and multivariate analysis in two retrospective series have suggested that the use of radiotherapy was correlated with better EFS and OS (Zinzani et al., 2001; Zinzani et al., 2002). However in the BCCA retrospective study, the introduction of routine radiotherapy to consolidate response after chemo-immunotherapy was not accompanied by any improvement in PFS and OS, even for initially bulky disease (Savage et al., 2006). The study from MSKCC which used radiotherapy in only 7% of patients treated with the NHL-15 regimen had excellent results, with OS = 84% at a median follow up of over 10 years. Also in the in the recent Greek retrospective study the use of RT in patients who responded to R-CHOP was associated with a statistically not different PFS (RT *vs.* non-RT: 92% *vs.* 93%) (Vassilakopoulos et al., 2012). Similarly, the excellent results that have been recently reported with DA-EPOCH-R has further strengthened this argument, with 93% EFS among 51 patients, only 2 of whom received radiotherapy have purported to negate the need for radiation in this disease. (Dunleavy et al., 2013) In the MD Anderson retrospective trial, recently reported by Pinnix et al. (Pinnix et al., 2015), 77 patients received standard R-CHOP (50) or R-HCVAD (27) followed by mediastinal RT in 42 (84%) and 17 (22%) respectively while 25 patients treated with R-EPOCH received consolidative RT only in 5 (20%). The 5 years PFS and OS rates for the entire group were 91% and 99% without any statistical differences between the 3 immunochemotherapy-regimen group.

6.5. Role of PET scan response assessment to guide the therapy choice

PET-CT after the completion of chemmoimmunotherapy is currently recommended for remission assessment in FDG avid lymphoma]. Visual interpretation of PET scan according to five-point score (Deauville criteria) has been validated as a reproducible method to assess responses. The Deauville score 1–3 represent a

Table 4
Rituximab based chemotherapy studies for primary mediastinal large B cell lymphoma (PMBCL).

Reference	No. Pts	Regimen	CR rate (%)	RFS (%)	OS (%)
Savage et al. (2006)	153	MACOP-B (47)	77[a]	69 (5 yrs)[a]	87 (5 yrs)
		CHOP (67)			71 (5 yrs)
		R-CHOP (19)			81 (5 yrs)
Zinzani et al. (2009)	45	R-V/MACOP-B + IFRT	62	88 (5 yrs)	80 (5 yrs)
Moskowitz et al. (2010)	54	R-CHOP14-ICE	82	78 (3 yrs)	88 (3 yrs)
Rieger et al. (2011)	87	CHOP-like (43)	54	64 (3 yrs)	78 (3 yrs)
		R-CHOP-like (44)	80	88 (3 yrs)	88 (3 yrs)
Vassilakopoulos et al. (2012)	120	R-CHOP (75)	90	81 (5 yrs)	91 (5 yrs)
		CHOP (45)	64	48 (5 yrs)	69 (5 yrs)
Dunleavy et al. (2013)	51	DA-EPOCH-R	94	93 (3 yrs)	97 (3 yrs)
Avigdor et al. (2014)	95	R-VACOP-B/R-CHOP (43)	82	79 (5 yrs)	97 (5 yrs)
		VACOP/B- CHOP (52)		58 (5 yrs)	88 (5 yrs)
Soumerai et al. (2014)	63	R-CHOP	71	68 (5 yrs)	79 (5 yrs)

[a] CR and RFS for the entire group of patients.

Complete Metabolic Response (CMR) in lymphoma patients treated with standard therapy (Barrington et al., 2014; Meignan et al., 2014). However, the studies performed to date in PMBCL have not yet fully clarified the role of PET-CT scan in the definition (CMR) and if whether consolidation radiotherapy might be spared on the basis of a negative PET-CT scan. In a retrospective study of 54 PMBCL patients treated with the R-CHOP/ICE dose-dense regimen without mediastinal RT, the Memorial Sloan-Kettering Cancer Center group reported 3-year OS and PFS of 88% and 78% respectively in patients who were PET negative at the end of the chemotherapy regimen (Moskowitz et al., 2010). In the BCCA study 96 PMBCL were treated with R-CHOP. Before 2005, consolidation RT to the mediastinum was routinely administered following R-CHOP, while after 2005, a PET/CT was planned at the end of chemotherapy to guide RT; if the PET was negative, patients were observed and if the PET was positive, consolidation RT was given if possible. Of 59 PET scans at the end of treatment, 35 (59%) were negative (2 received RT) and 24 (41%) were positive (23 received RT).With a median follow-up of more than 5 years, there was no survival difference between PET-negative and PET-positive cases, suggesting that a PET-guided RT approach in R-CHOP-treated PMBCL may reduce the use of RT (Savage et al., 2012). Similar results have been reported (Zinzani et al., 2015) in an Italian retrospective series of 74 PMBCL patients treated with R-MACOP-B. At the end of chemo-immunotherapy 51 (61%) resulted PET positive received mediastinal RT while the remaining 23 (39%) PET negative did not receive RT. No significant differences in 5-years EFS (91% vs. 90%) were found between PET negative and PET positive cases.

To assess the role of PET/CT after chemoimmunotherapy in patients with PMBCL the IELSG started in 2007 a prospective study phase II (IELSG 26 study). Among 125 patients prospectively enrolled, 115 were eligible for central review of PET/CT scans at the completion of standard chemo-immunotherapy using the Deauville five-point score (5PS) 89% of these patients received also a consolidation RT. Fifty-four patients (47%) achieved a CMR, defined as a completely negative scan or with residual 18-FDG activity below the mediastinal blood pool (MBP) uptake (score 1–2). In the remaining 61 patients (53%), the residual uptake was higher than MBP but below the liver uptake (score 3) in 27 (23%), slightly and markedly higher than the liver uptake (score 4–5) in 34 (30%). Patients with residual uptake higher than MBP but below liver (score 3) had equally good outcomes, without any recurrence. Using the liver uptake as cut-off for PET positivity (score 4–5) discriminated most effectively between high or low risk of failure, with 5-year PFS of 99% *vs.* 68% ($p < 0.0001$) and 5-year OS of 100% *vs.* 83% ($p = 0.0003$) (Martelli et al., 2014).

These results were confirmed in another Italian study where 80 PMBCL treated of a rituximab based chemotherapy underwent PET at the end of chemotherapy. Patients with PET Deauville score 1–3 had an improved 3 years OS (100% *vs.* 77%; $p < 0.05$) compared to patients with a score of 4–5, however all patients received a consolidation mediastinal RT irrespective of PET result (Filippi et al., 2013). Also in the MD Anderson series patients with a 5PS score 4–5 after chemoimmunotherapy experienced a worse outcome if compared with 5PS 1–3 (Pinnix et al., 2015). Recently Ceriani et al. reported the results of the post consolidative mediastinal RT, in 88 patients with PMBCL enrolled in the phase II IELSG 26 prospective trial. All the patients obtaining a CMR (PS = 1-2, 68 pts) or an higher MBP but below the liver uptake (PS = 3, 10 pts) remain progression free at 5-years. Among the 10 patients (11%) with persistent slight higher positive scan (DS = 4, 6 pts) or markedly higher than liver uptake (PS = 5, 4 pts) the PFS and OS were significant poorer. Of interest DS = 5 (75%) patients had subsequent disease recurrence while the 6 patients DS = 4 had a good outcome without recurrence (Ceriani et al., 2017).

In the group of patients treated with the DA-EPOCH-R regimen 50% of patients showed a PET-positivity, defined by FDG uptake greater than the MBP at the completion of chemo immunotherapy, but only 3/18 had progressive disease without the use of consolidation radiotherapy (Dunleavy et al., 2013).

These data indicate that PET-TC scan in PMBCL has an excellent negative predictive value but limited positive predictive value due to high frequency of positive scans. This false positive rate in particular requires further definition before modifying planned therapy based upon FDG-PET evaluation alone in PMBCL, although de-escalation of therapy based upon the finding of a negative FDG-PET scan is entering clinical practice. It has been suggested that an inflammatory response produced by the addition of rituximab to chemotherapy or a thymic rebound, which is particularly relevant given the location of the disease and their generally young age, may cause increased FDG uptake and thus reduce PPV and specificity. For this reason an international phase III randomized trial (IELSG 37) is now ongoing to assess the role of consolidation RT in PMBCL patients with PET-negative mediastinal masses after standard chemo-immunotherapy. The trial should be able to demonstrate a non-inferior outcome in patients not receiving RT5. The study may eventually allow to individualise treatment for each patient by adapting it to the PET response limiting the indication for additional radiotherapy only to the PET positive patients with an inadequate response to chemoimmunotherapy (Martelli et al., 2013).

In the IELSG 26 study we have also measured, in 103 out of 125 patients the value of SUV, metabolic tumour volume (MTV), and total lesions glycolysis (TLG) at the baseline PET-CT scans according to the standard protocol. At 5-years OS was 100% for patients with low TLG compared to 80% for those with high TLG ($p = 0.0001$) while PFS was 97% *vs.* 64%, respectively ($p < 0.0001$). The value of TLG on

baseline PET scan outcome should be considered in future studies as powerful predictor of PMBCL (Ceriani et al., 2015).

6.6. Consolidation high dose chemotherapy and transplant

The relatively young age and low frequency of bone marrow involvement of the PMBCL patient population are the basis for consideration of high-dose therapy (HDT) and peripheral blood stem cells transplantation (PBSCT) to consolidate first remission. In the GELTAMO series 35 patients in first CR, but considered at "high-risk" of relapse, underwent HDT with various preparative regimens. At 4 years, the overall survival and PFS were 84% and 81%, respectively (Rodriguez et al., 2008). In the Memorial Sloan- Kettering experience, HDT with progenitor cell rescue at first remission was not superior to dose-dense sequential therapy. Based on the results obtained with R-CHOP/MACOP-B with/without mediastinal RT or with more intensive chemo-immunotherapy regimen as DA-EPOCH-R, that appear comparable with the reports of HDT-ASCT as consolidation first line therapy, there is no good evidence to recommend a HDT to consolidate first CR, even in poor-risk patients. The HDT-ASCT should be reserved to those patients whose lymphoma progress or obtain an inadequate response during first-line therapy.

6.7. Treatment of relapsed or refractory disease

The probability of recurrence after successful initial therapy for PMBCL appears to be lower than that of DLBCL, this may reflect the earlier stage at presentation, the younger age or possibly the biology of the disease. Patients with PMBCL who achieve a response lasting longer than 18 months after diagnosis are likely to be cured. Treatment failure usually occurs either during initial treatment or within the first 6 to12 months after completion of treatment. PMBCL, can either recur locally in the mediastinum or can spread to parenchymal organs especially in extranodal sites as surrenal glands kidneys, ovary and liver. Bone marrow involvement and CNS are rare even at the time of recurrence. Although the outcome of relapsed/refractory PMBCL is considered very poor, HDT-ASCT may improve survival (Kuruvilla et al., 2008; Sehn et al., 1998). Treatment strategies are similar to those used for other DLBCL, testing chemosensitivity with a salvage chemotherapy regimen (R-DHAP, R-ICE others) followed by consolidation with HDT-ASCT (Gisselbrecht et al., 2010). Among patients who undergo to HDT-ASCT patients with relapsed disease have a greater survival if compared to refractory disease. Salvage R-chemotherapy regimen and RT (if not administered as upfront therapy) followed by HDT-ASCT should be considered the standard therapy for relapsed/refractory PMBCL patients.

6.8. Novel therapies

JAK-STAT pathway deregulation is the hallmark of PMBCL and cHL, and positively regulates the expression of PDL1 and PDL2. PDL1 and PDL2 overexpression are instrumental in PMBCL to survive in the thymic microenviroment. JAK inhibitors switch off PDL expression and downmodulate the canonical JAK-STAT signalling. The results of these studies have shed light in to the biology of PMBCL and some of the dysregulated molecular mechanisms described above will become a preclinical model for a possible role for novel agents such as anti PD1-PDL1 antibodies, JAK2 inhibitors, bortezomib or other molecule kappa kinases inhibitor and brentuximab vedotin. Pidilizumab (humanized IgG-1 recombinant monoclonal antibody) and Nivolumab (fully humanized IgG-4 monoclonal antibody) directed on the PD-1 receptor has shown a significant activity in relapsed/refractory HD (Ansell et al., 2015) and promising results in phase I-Ib trials for relapsed/refractory non-Hodgkin lymphoma (Lesokin et al., 2014). A phase II trial is currently registered on clinicaltrials.gov for Nivolumab in patients with relapsed/refractory DLBCL/PMBCL who failed ASCT or two prior standard regimens and are transplant ineligible (ClinicalTrials.gov Identifier: NCT02038933). A phase II of brentuximab vedotin in CD30 positive DLBCL resulted in a complete response rate of 16% in 6 relapsed/refractory PMBCL patients. In this study, CD30 expression did not correlate with the response rate (Bartlett et al., 2013).

Conflict of interest disclosure

the authors declare that they have no conflict of interest.

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