Primary Mediastinal Large B-Cell Lymphoma

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Peter Johnson, Jan Delabie, Scott Rodig, and Maurizio Martelli

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Pathology: Jan Delabie and Scott Rodig

P. Johnson (✉)
Cancer Research UK Centre,
University Hospital Southampton, Southampton, UK
e-mail: johnsonp@soton.ac.uk

J. Delabie, MD
Department of Pathology, Oslo University Hospital,
Oslo, Norway
e-mail: jandel@ous-hf.no

S. Rodig, MD
Department of Pathology,
Brigham and Women's Hospital,
Harvard Medical School, Boston, MA, USA
e-mail: srodig@partners.org

M. Martelli
Division of Hematology, Department of Cellular Biotechnologies and Hematology,
Sapienza University of Rome, Rome, Italy
e-mail: martelli@bce.uniroma1.it

10.1 Introduction

Primary mediastinal large B-cell lymphoma (PMBCL) was first described in the 1980s (Lichtenstein et al. 1980; Levitt et al. 1982). It is a relatively uncommon clinicopathologic entity specifically recognised in the WHO classification of lymphoid malignancies (Harris et al. 1994; Harris et al. 1999). This malignancy is characterised by aggressive and locally invasive behaviour. Although in some respects it resembles nodal diffuse large B-cell lymphoma (DLBCL), it has distinct epidemiologic, morphologic, immunophenotypic, and clinical features. This lymphoma is a DLBCL that arises in the thymus from a putative thymic peripheral B cell.

10.2 Epidemiology

Primary mediastinal large B-cell lymphoma constitutes 2–4 % of non-Hodgkin lymphoma (NHL) and 6–10 % of diffuse large B-cell lymphomas (DLBCL) (Levitt et al. 1982; Harris et al. 1994).

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It is found worldwide (Cazals-Hatem et al. 1996; Armitage and Weisenburger 1998). It is more common in young adults (median age 35–40 years) with a female predominance and originates in the mediastinum, where it frequently presents with features of local invasion. No particular genetic or environmental risk factors have been clearly identified.

10.3 Pathology and Biology

The diagnosis of PMBCL is based on the integration of morphologic, immunophenotypic, genetic, and clinical data, according to the WHO classification, with the differential diagnosis mainly includes classical Hodgkin lymphoma (cHL), mediastinal grey zone lymphoma (MGZL), and other DLBCL subtypes, from which it cannot be reliably distinguished in some cases.

10.3.1 Cell of Origin

It is postulated that PMBCL derives from the small subset of thymic B cells with asteroid shape located around the Hassall's corpuscles in the medullary thymus which share with PMBCL a CD10-,CD21-,CD23+-phenotype. The clinical presentation within the anterior mediastinum and the identification of normal thymic cells that express the MAL protein support this hypothesis (Copie-Bergman et al. 2002).

10.3.2 Histopathology

Primary mediastinal large B-cell lymphoma has distinct morphological and phenotypic features. It is typically associated with compartmentalising alveolar fibrosis in the vast majority of cases (Moller et al. 1986; Cazals-Hatem et al. 1996; Paulli et al. 1999); however, this can vary from case to case and from field to field within the same specimen. The fibrosis tends to surround groups of lymphomatous elements, producing compartmentalisation of the neoplastic growth. In cases when thick collagen bands enclose clusters of neoplastic cells, the sclerosis is readily appreciated on hematoxylin- and eosin-stained sections. Tumour cells are large and polymorphic with rather abundant clear cytoplasm, and nuclei may be lobulated with prominent eosinophilic nucleoli. Not infrequently, Reed-Sternberg-like cells may be seen. In such instances, careful immunohistochemical evaluation is warranted in order to exclude the diagnosis of cHL. 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 (Moller et al. 1986; Paulli et al. 1999; Barth et al. 2002; Traverse-Glehen et al. 2005).

10.3.3 Immunophenotype

On immunophenotypic analysis, despite generally lacking surface and cytoplasmic immunoglobulin (Ig), PMBCL expresses B-cell-related antigens such as CD19, CD20, CD22, CD79a (at times variable), and PAX5 as well as the leukocyte common antigen (CD45) (Moller et al. 1986; Barth et al. 2002; Pileri et al. 2003; Loddenkemper et al. 2004). CD30 staining is observed in the vast majority of cases (~80 %), although it is weaker and less homogeneous than in cHL and anaplastic large-cell lymphoma (Pileri et al. 2003). CD15 is occasionally present. Tumour cells are more frequently positive for IRF4 (75 %), BCL2 (55–80 %), and CD23 (70 %), whilst BCL6 expression is variable (45–100 %) and CD10 is more often negative (8–32 %) (de Leval et al. 2001; Pileri et al. 2003). Tumour cells are often MAL positive, as a consequence of MAL gene overexpression (Copie-Bergman et al. 1999). The latter is located on the long arm of chromosome 2 and encodes a protein thought to play a role in membrane trafficking and signalling (Millan and Alonso 1998), which might contribute to pathogenesis. Furthermore, PMBCL usually expresses BOB1, PU1, and OCT2, co-expresses TRAF1, and presents with nuclear REL (Copie-Bergman et al. 2002; Copie-Bergman et al. 2003; Pileri et al. 2003; Rodig et al. 2007) (Fig. 10.1).

10.3.4 Diagnostic Criteria

The main differential diagnoses are classical Hodgkin lymphoma and diffuse large B-cell lymphoma (Table 10.1). Classical Hodgkin lymphoma can be distinguished from PMBCL by histological features such as abundant infiltration with granulocytes and small sized lymphocytes as well as histiocytes in the former. In addition, classical Hodgkin lymphoma expresses CD15 and less often a full set of B-cell markers. The B-cell transcription factor PAX5 is only weakly expressed in Hodgkin lymphoma, in contrast to PMBCL. MAL has been reported to be specifically expressed in PMBCL but is rather a difficult marker to stain for in routine practice (Copie-Bergman et al. 2002). Some cases with either morphological features of PMBCL but immunophenotypical features of classical Hodgkin lymphoma or vice versa do not allow a final diagnosis and are classified as B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma, or the so-called mediastinal grey zone lymphoma (Traverse-Glehen et al. 2005). The differential diagnosis with diffuse large B-cell lymphoma, 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 (Calaminici et al. 2004). Recently, it was also demonstrated that immunohistochemical

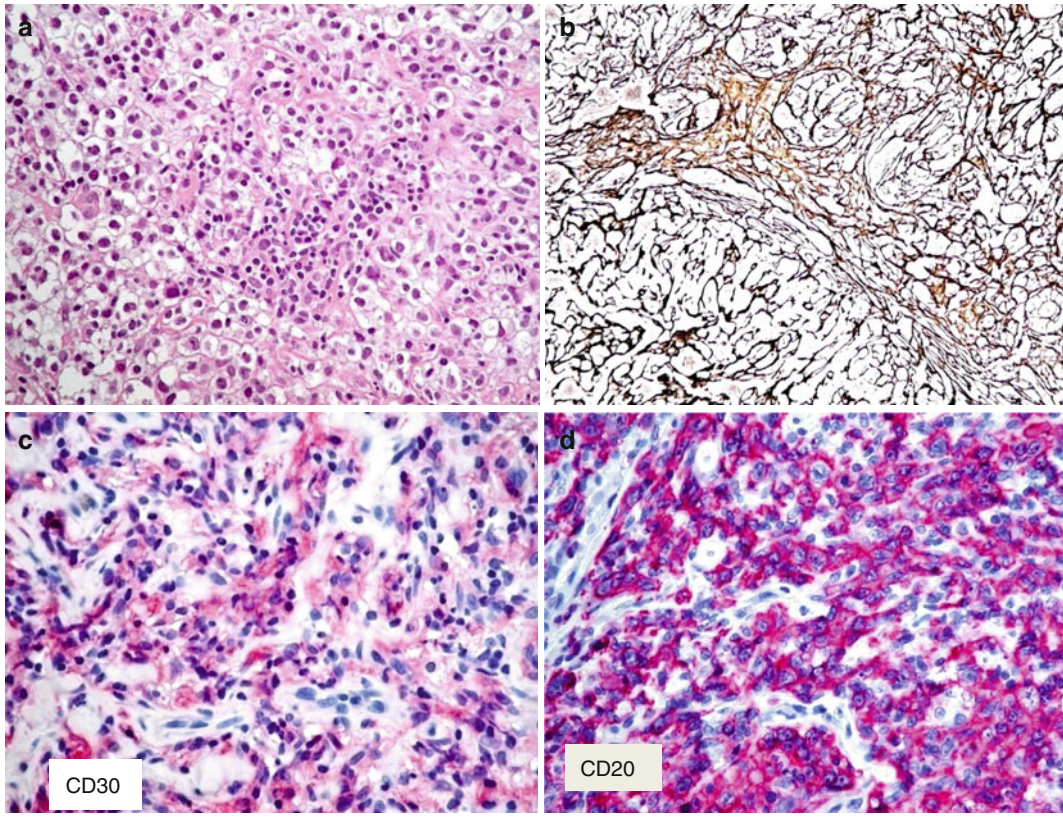

Fig. 10.1 Primary mediastinal B-cell lymphoma: (**a**) H&E staining, consists of the neoplastic large cells with clear cytoplasm, (**b**) fibrotic bands with compartmentalising alveolar fibrosis, (**c**) tumour cells express CD30 on their membrane, (**d**) typically shows CD20-positive cells, (**e**) tumour cells also show strong cytoplasmic staining for MAL antigen, (**f**) tumour cells are frequently BCL6 and IRF4 positive, (**g**) surface and cytoplasmic staining for immunoglobulin are mostly negative, and (**h**) the transcription factors OCT-2 and BOB-1 are usually expressed (Reprinted from Pileri et al. (2003). With the permission)

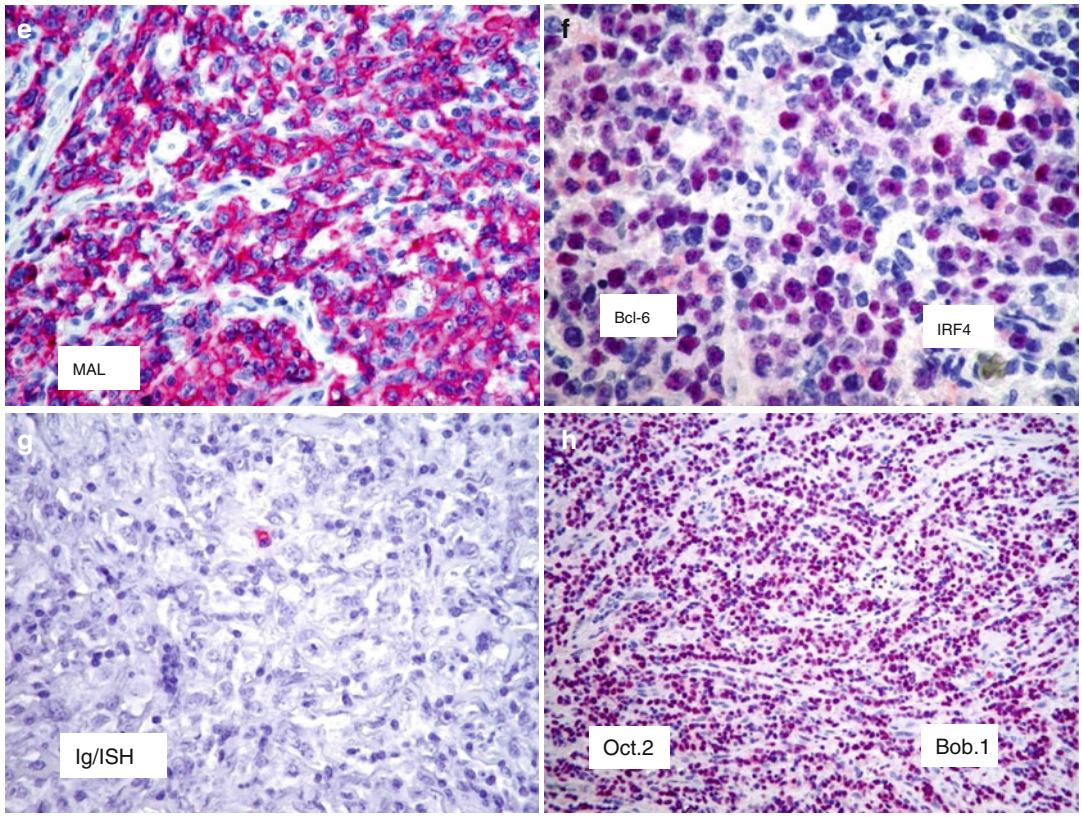

Fig. 10.1 (continued)

Table 10.1 Comparison of the pathological and immunophenotype features of primary mediastinal large B-cell lymphoma (PMBCL), diffuse large B-cell lymphoma (DLBCL), nodular sclerosis classical Hodgkin lymphoma (NScHD), and mediastinal grey zone lymphoma (MGZL)

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

analysis of TNFAIP2, expressed by most cases of PMBCL and Hodgkin lymphoma but not by diffuse large B-cell lymphoma, NOS, may be useful for making a correct diagnosis (Kondratiev et al. 2011). Gene expression analysis allows for an improved distinction between PMBCL and diffuse large B-cell lymphoma, NOS, but can as yet not be used in clinical practice (Rosenwald et al. 2003).

10.3.5 Genetic Characteristics

Gene alterations are diverse, and copy number gains of REL, PDL1/PDL2, JAK2, and JMJD2C; chromosomal rearrangement of CIITA; mutations of SOCS1, STAT6, TNFAIP3, MYC, and TP53; or promotor hypermethylation of p16/INK may be seen (Steidl and Gascoyne 2011). The common consequences of these changes are activation of JAK-STAT signalling and NFkB pathways, resulting in increased cell proliferation and survival. In addition, downregulation of HLA class II molecules as well as overexpression of PD-1 ligands as a consequence of the genetic changes cited above may allow PMBCL to escape immune surveillance. Interestingly, gene expression studies have shown a remarkable overlap of highly expressed genes and gene changes between PMBCL and Hodgkin lymphoma (Rosenwald et al. 2003; Steidl and Gascoyne 2011). Not surprisingly, the differential diagnosis between PMBCL and mediastinal Hodgkin lymphoma can be difficult and virtually impossible in some cases (Traverse-Glehen et al. 2005). The latter cases are called B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma, and classical Hodgkin lymphoma, also known as "mediastinal grey zone lymphoma."

10.4 Clinical Presentation

10.4.1 Clinical Features

Primary mediastinal large B-cell lymphoma normally presents with a bulky tumour in the anterior mediastinum that is rapidly progressive and gives rise to local compressive effects including dyspnea, cough, dysphagia, and superior vena cava obstruction. 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. The mediastinal tumour is frequently bulky, being over 10 cm in two-thirds of patients, and infiltrating the lung, chest wall, pleura, and pericardium (Falini et al. 1995; Armitage and Weisenburger 1998). Pleural or pericardial effusions are present in one-third of cases (Lazzarino et al. 1997; Zinzani et al. 2001). Breast oedema is common, and hoarseness may reflect recurrent laryngeal nerve damage (Fig. 10.2). Despite the local invasiveness, distant spread is infrequent at the outset, and even spread to the supraclavicular nodes is unusual at presentation. Extranodal sites may, however, be involved, particularly in cases of disease recurrence, with an unusual propensity for involvement of the kidneys, adrenal glands, liver, and ovaries (Haioun et al. 1989; Lazzarino et al. 1993; Bishop et al. 1999). Systemic symptoms, mainly fever or weight loss, are present in a minority of cases. Bone marrow infiltration at presentation is rare, but elevated lactate dehydrogenase levels are observed in two-thirds of patients. MGZL shows similar clinical features but, compared to PMBCL, is more common in young men and more often has extranodal involvement (Table 10.2).

10.4.2 Diagnostic and Staging Procedures

The complete staging workup for PMBCL is the same as that routinely used for nodal lymphoma. It includes an accurate physical examination, complete hematologic and biochemical examinations, total body computerised tomography, and bone marrow biopsy. The staging system used is the standard Ann Arbor classification (Carbone et al. 1971). A diagnostic tissue sample can be obtained by mediastinoscopy, biopsy of the tumour mass through the supraclavicular fossa,

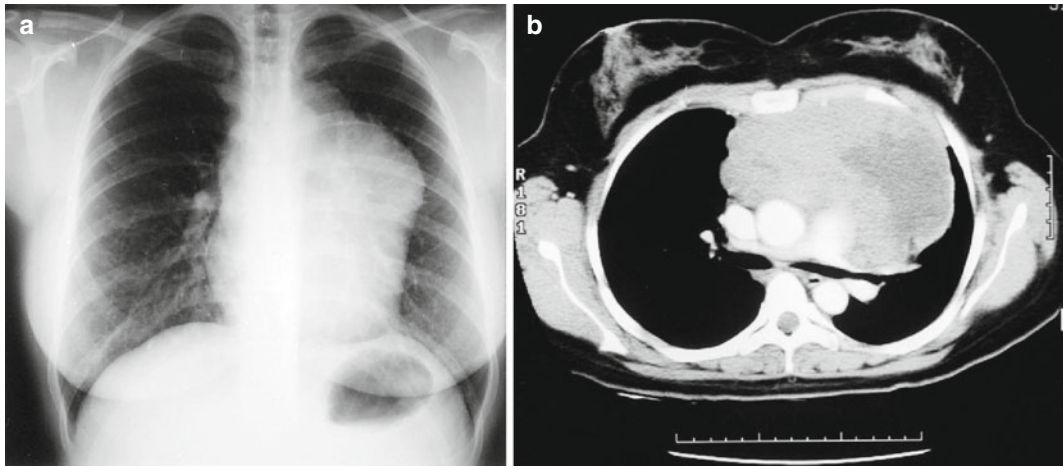

Fig. 10.2 CXR (**a**) and CT (**b**) scan from a female patient presenting with PMBCL. Note the large anterior mediastinal mass, with areas suggestive of central necrosis. Marked breast oedema is present

Table 10.2 Comparison of the clinical features of: primary mediastinal large B-cell lymphoma (PMBCL), diffuse large B-cell lymphoma (DLBCL), nodular sclerosis classical Hodgkin lymphoma (NScHD), and mediastinal grey zone lymphoma (MGZL)

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

anterior mediastinotomy, or minithoracotomy. It is important to consider the anaesthetic risk for patients with critical airways narrowing by anterior mediastinal tumours: it may be preferable to obtain a needle core biopsy by a percutaneous route under local anaesthesia than to obtain a large biopsy but have a patient who cannot be extubated following the procedure because of airway compromise.

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 characterise 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.

10.4.3 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 (Abou-Elella et al. 1999). 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 2E when

contiguous extranodal sites such as the lung are involved (Todeschini et al. 2004; Hamlin et al. 2005; Savage et al. 2006). Elevated LDH to more than twice the upper limit of normal, age over 40, and performance status ≥2 all correlated with reduced survival in a population-based series from British Columbia (Savage et al. 2006), whilst 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 (Zinzani et al. 2002). Recent gene expression studies have suggested that low expression of major histocompatibility (MHC) class II genes correlate with a poor outcome (Roberts et al. 2006).

10.5 Treatment and Outcome

The first line of treatment and its outcome are critical in managing PMBCL. Therapy for recurrence or progressive disease is of strictly limited efficacy (Todeschini et al. 2004; Savage et al. 2006; Kuruvilla et al. 2008) making curative therapy at the first attempt even more important for this type of lymphoma. It is, however, important to strike an appropriate balance between the delivery of the highest possible cure fraction and minimising the long-term morbidity for this young population. A number of choices have to be made, including the initial chemotherapy/immunochemotherapy and whether there might be a benefit from high-dose therapy in first remission. The role of consolidation radiotherapy to the mediastinum is especially controversial.

10.5.1 Choice of Initial Treatment Regimen

There is broad agreement that for conventional DLBCL, the standard of care is the R-CHOP regimen. Prior to the introduction of rituximab, no advantage was demonstrated for the use of third-generation anthracycline-containing regimens over conventional CHOP for DLBCL in general (Fisher et al. 1993), but some retrospective series in PMBCL suggested that superior outcomes might be achieved with latter generation regimens (Todeschini et al. 2004). The largest series was from the IELSG, which reviewed the outcomes of 426 previously untreated patients with PMBCL (Zinzani et al. 2002). Most of the patients that were treated with a third-generation regimen received MACOP-B ($n=204$), the rest either VACOP-B ($n=34$) or ProMACE CytaBOM ($n=39$). Although the complete response rate was similar between the third-generation subgroup and those treated with conventional CHOP or CHOP-B, the relapse rate at 3 years was significantly lower in the third-generation group (12 % vs. 23 %; $P=0.02$), and the projected 10-year overall and progression-free survival were superior at 71 and 67 %, compared to 44 and 33 % ($P=0.0001$ and $P=0.0003$, respectively). The British Columbia group carried out a population-based retrospective analysis of 153 patients with PMBCL whose treatment was determined by era-specific guidelines (Savage et al. 2006). Between 1980 and 1992 MACOP-B or VACOP-B was used, switching to CHOP between 1992 and 2001 and then to rituximab with CHOP (R-CHOP) thereafter. The overall survival for the cohort was 75 % at 5 years, with the overall survival at 5 years being 87 % for those treated with MACOP-B/VACOP-B, significantly higher than the 71 % for those patients treated with CHOP ($P=0.048$). Comparison of the baseline characteristics, however, demonstrated a greater number of poor risk patients in the CHOP group. In the multivariate analysis for overall survival, the type of chemotherapy regimen showed a trend towards improved outcomes, but this was not statistically significant.

10.5.2 The Addition of Rituximab to Chemotherapy

It is generally accepted that the addition of rituximab to chemotherapy for PMBL yields superior results. The MiNT study compared the outcomes for 824 patients with low-risk large B-cell lymphoma randomised to receive CHOP-like chemotherapy with or without rituximab (Pfreundschuh et al. 2006), which included a subset of 87

patients with PMBCL. The addition of rituximab increased the CR rate from 54 to 80 % and the 3-year event-free survival from 52 to 78 % ($p=0.012$). The difference in overall survival did not reach statistical significance owing to the small number with PMBCL (3-year OS 78 vs. 89 %, $p=0.16$), but was of the same order as that seen for the whole trial (85 % vs. 93 %, $p<0.001$) (Rieger et al. 2011). The addition of rituximab to dose-adjusted EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone) in small numbers of patients with PMBL has also been reported as showing a favourable event-free ($P=0.036$) and overall survival ($P=0.023$) in a non-randomised comparison (Dunleavy et al. 2006). In a small series from Israel, the addition of rituximab appeared to improve progression-free survival, particularly in those patients receiving CHOP, whilst there was no difference in outcomes in a comparison between either a third-generation regimen with rituximab or CHOP with rituximab (R-VACOP-B vs. R-CHOP, 84 % and 74 %, respectively; $P=0.44$) (Avigdor et al. 2007). 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 large B-cell lymphoma.

10.5.3 Assessment of the Response to Initial Therapy

The presence of bulky masses at the time of diagnosis, together with the extensive fibrotic elements of PMBL, often results in a residual mediastinal mass being present at the completion of initial chemotherapy. It may be difficult to distinguish inert fibrous tissue from viable residual lymphoma on conventional cross-sectional imaging, and for this reason, functional imaging has been extensively investigated. The ^{67}gallium scan was found to have predictive value for PMBL in identifying patients at risk of relapse (Zinzani et al. 1999); however, it is time consuming to perform and has poor spatial resolution. The ^{18}Fluoro-Deoxy-Glucose Positron Emission Tomography (FDG-PET) scan has become the investigation of choice for residual masses in PMBCL, although there is some uncertainty about its positive predictive value in particular. A systematic review of FDG-PET studies has examined post-therapy response assessment in lymphoma (Terasawa et al. 2008). In the studies reporting evaluation of residual masses in aggressive NHL, the demonstrated sensitivity of PET ranged from 33 to 87 % and the specificity from 75 to 100 %. A prospective study of FDG-PET scanning in patients with PMBCL after 4 cycles of accelerated (14 days) R-CHOP performed at Memorial Sloan Kettering Cancer Center showed that among 14 patients with interim positive PET scans, none had viable lymphoma present on biopsy, and all remained in remission after completing consolidation R-ICE chemotherapy (Moskowitz et al. 2010). A prospective study of FDG-PET scanning 125 patients with PMBCL conducted by the IELSG yielded a relatively low rate of negative scans at under 50 % despite excellent clinical outcomes, albeit after the use of consolidation radiotherapy in 123 cases (Martelli et al. 2011). These data indicate that further evaluation is required before modifying planned therapy based upon FDG-PET evaluation alone in PMBCL. The false-positive rate in particular requires definition, although de-escalation of therapy based upon the finding of a negative FDG-PET scan is entering clinical practice and is the subject of a prospective randomised trial.

10.5.4 The Role of Consolidation Radiotherapy

Irradiation of the mediastinum is one of the most controversial aspects of the management of PMBCL. 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 (Todeschini et al. 2004; Mazzarotto et al. 2007; De Sanctis et al. 2008). It is clear from the IELSG series that many patients completing chemotherapy in PR may be converted to CR following radiotherapy (Zinzani et al. 2002), that radiotherapy may render active residual mediastinal masses ^{67}gallium negative (Zinzani et al. 1999), or result in long-term remission after a positive FDG-PET scan (Martelli et al. 2011). Univariate and multivariate analyses in two retrospective series have suggested that the use of radiotherapy was correlated with better event-free and overall survival (Todeschini et al. 2004; Rodriguez et al. 2008).

Those who would prefer to avoid irradiation of the mediastinum can however point to good results in studies that have used chemotherapy alone (Cazals-Hatem et al. 1996; Hamlin et al. 2005; Dunleavy et al. 2013; Massoud et al. 2008). In British Columbia, the introduction of routine radiotherapy to consolidate response after chemotherapy was not accompanied by any improvement in progression-free or overall survival, even for initially bulky disease (Savage et al. 2006). The study from Memorial Sloan Kettering Cancer Center which used radiotherapy in only 7 % of patients treated with the NHL-15 regimen (comprising intensified doxorubicin, vincristine, and cyclophosphamide) had excellent results, with overall survival of 84 % at a median follow-up of over 10 years (Hamlin et al. 2005). The results that have been reported with dose-adjusted EPOCH in combination with rituximab are also claimed to negate the need for irradiation (Dunleavy et al. 2013).

It is clear that further research is needed in order to determine the safety of omitting radiation in patients with non-FDG avid mediastinal masses at the completion of chemotherapy.

10.5.5 Intensification with High-Dose Therapy at First Remission

Before the widespread use of consolidation radiotherapy to the mediastinum, the results with PMBCL were thought to be inferior to those of other types of DLBCL, and this, together with the rarity of marrow involvement and the younger age of PMBCL patients, led to the testing of high-dose chemotherapy and peripheral blood progenitor rescue at first remission. The largest series reported comes from the GEL-TAMO registry (Rodriguez et al. 2008). Thirty-five patients in first CR, but considered at 'high-risk' of relapse, underwent high-dose therapy with variable conditioning regimens. At 4 years, the overall and progression-free survival were 84 and 81 %, respectively, similar to the results seen among 12 patients (8 in CR and 4 in PR) reported by Sehn et al. (1998). Just over half the patients in the GEL-TAMO series also received irradiation either before or after high-dose therapy, and this was one of the dominant variables associated with overall survival in multivariate analysis. In the IELSG analysis, a limited number of patients ($n=44$) underwent high-dose therapy which resulted in an estimated overall survival of 77 % at 10 years (Zinzani et al. 2002). In the Memorial Sloan Kettering experience high-dose therapy with progenitor cell rescue at first remission was not superior to dose-dense sequential therapy (Hamlin et al. 2005).

Taken overall, the results now obtained with R-CHOP and consolidation radiotherapy to the mediastinum appear favourable by comparison with the reports of high-dose consolidation, which is not widely used at first remission in other types of DLBCL. At present, there is no good evidence to support its use in this context for PMBCL.

The exception to this may be those patients whose lymphomas progress during primary therapy. These have a very poor outlook: of 14 patients in the British Columbia series, the majority were resistant to alternative chemotherapy regimens, and there were no long-term survivors (Savage et al. 2006). Sehn et al. however reported on 12 patients with refractory disease who at 5 years had a progression-free survival of 58 % following high-dose chemotherapy (Sehn et al. 1998). It is appropriate in this setting to test chemosensitivity to a second-line regimen prior to myeloablative treatment, proceed in those fit

enough to do so, and consolidate the response with involved field radiotherapy.

10.5.6 Treatment of Recurrent Disease

The probability of recurrence after successful initial therapy for PMBCL appears to be lower than that of DLBL in general, although this may reflect the earlier stage at presentation, the younger age, or possibly the biology of the disease. Most recurrences occur within the first year, and they are rare beyond two years from completion of therapy (Zinzani et al. 1999; Todeschini et al. 2004; Savage et al. 2006). Extranodal sites of recurrence are not uncommon, especially the kidneys and spleen, but spread to the central nervous system is highly unusual (Papageorgiou et al. 2012).

Second-line treatment strategies are similar to those used for DLBCL, attempting reinduction with non-cross-resistant agents, followed by consolidation with high-dose chemotherapy in those with a good response who remain fit enough. In general, the outcomes have been disappointing. In one series of 138 patients, all those who relapsed died from their lymphoma (Todeschini et al. 2004), although another series from the MD Anderson Cancer Center had 42 % long-term survivors (Popat et al. 1998). The general use of rituximab in first-line therapy has made recurrence less frequent but harder to manage successfully.

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