

Case Report

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Case Study: Management of a patient with Primary Mediastinal B-cell Lymphoma (PMBL)

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Citation: Taqaddas A (2020) Case Study: Management of a patient with Primary Mediastinal B-cell Lymphoma (PMBL). J Can Res Adv Ther 1(1): 13-21.

Received Date: June 03, 2020; **Accepted Date:** June 20, 2020; **Published Date:** June 22, 2020

Abstract

This case study discusses oncological management of a patient with Primary Mediastinal B-cell Lymphoma focusing on radiotherapy treatment. Secondary objective of this study is to find out how management of PMBL has evolved since 2006

Introduction

Lymphomas are neoplasms of lymphocytes and their precursor cells [1]. Malignant lymphomas can be broadly divided into Hodgkin's disease and Non-Hodgkin's lymphoma – NHL [2]. The incidence of NHL is rising worldwide and is the 5th most common malignancy in United States [3]. In UK, NHL accounts for 2.4% of all cancers registered in England and Wales and 2.6% of all cancer deaths [4] NHL may arise in lymph nodes as well as at a wide variety of extra-nodal sites [5]. The most common lymphomas are of diffuse large B-cell type -DLBCL (33%) followed by B-cell follicular lymphomas [4]. Primary Mediastinal B-cell Lymphoma (PMBL) is a subtype of diffuse large B cell NHL. DLBCL are considered intermediate grade NHL. The aim of this case study is to discuss management of a patient with primary Mediastinal B-cell lymphoma focusing on the management of the disease. However, it will include a general overview of diagnostic workup, staging, prognostic factors and implications for professional practice. The principal investigator carried out this case study in 2006 while student of Therapeutic radiography and had access to patient cases in accordance to institutional and university standard procedures. The author also intends to see how the management of PMBL has evolved since 2006 i.e. in what respects the management of these patients these days differ from the past practices.

Patient selection and Ethical approval

Patient was retrospectively selected from Electronic patient

record system i.e. from hospital clinical database. Patient case history was retrieved from case records in compliance with hospital policies and UK data protection act, as a result specific research ethics approval was not required. It is a standard procedure for hospital/university students under training to have access to patient records for case study, research and educational purposes. Consequently, again no ethical approval was required.

The patient and clinical presentation

A 65 years old gentleman with a diagnosis of a stage11a primary mediastinal diffuse B-cell lymphoma (a type of NHL) presented with one-month history of hoarse voice and a short history of a swollen right arm and a puffy face and neck. On admission he was diagnosed with Superior vena cava syndrome. No episodes of night sweats or weight loss were reported. Later CT imaging demonstrated a mass in superior mediastinum and adenopathy. PMBL is the commonest mediastinal lymphoma in adults and presents with the typical symptoms of an anterior mediastinal mass, cough, dysphagia, hoarse voice, chest pain and superior vena cava obstruction- SVCO [5]. Souhami and Tobias further state that enlarging mass (nodal/extra-nodal) causes initial symptoms due to compression e.g. swelling of arm or leg simulating SVCO [5]. Besien and colleague [6] state superior vena cava syndrome is the most common symptom at diagnosis and occurs in about 30% of patients.

Magrath state that one of the most common symptoms of lymphoma is swelling of peripheral lymph nodes (LNs) or

symptoms (pain/swelling) relating to a mass (nodal/extranodal) in the abdomen or chest [1]. He further mentions facial swelling as one of the symptoms. Other symptoms of NHL include hepatosplenomegaly, fatigue, night sweats, weight loss, itching, breathlessness, bruising, recurrent infection and bone pain [4].

Diagnostic Workup

A number of investigations were carried out to diagnosis, stage and grade the disease as well as to decide on an appropriate and effective treatment plan. Investigations were also performed to determine the response to initial treatment. These investigations are discussed below.

History and Physical examination (PE)

There was no history of B symptoms such as fever, night sweats and weight loss. A detailed physical examination of all lymph nodes was performed. Abdominal examination was unremarkable. There was a previous history of DVT (Deep vein thrombosis) of right internal jugular and right subclavian vein and therefore the patient was on Warfarin. The patient had a hoarse voice as a result of pressure on the right recurrent laryngeal nerve.

Laboratory Studies

Full blood count including erythrocyte sedimentation rate, serum lactate dehydrogenase and B2 microglobulin measurement and serum electrolytes, urea and creatinine assessment was done. The blood urea and electrolytes are measured to exclude renal failure. Liver function test was performed by measuring liver enzymes. A rise in alkaline phosphatase, transaminases may indicate liver infiltration [5].

Radiographic Imaging

Chest x-ray was clear. Besides Hilar, mediastinal or paratracheal nodal enlargement, a chest x-ray may detect parenchymal lung lesions and pleural effusion as later more frequently occurs when there is massive mediastinal disease [5]. A CT scan of neck, thorax, abdomen and pelvis demonstrated a 5.1 * 3.2cm mass in the superior mediastinum and a 9mm subcarinal lymph node. A pretracheal lymph node and a further mediastinal lymph node at the superior level of aortic arch were noted. Presently CT is the main imaging modality for diagnosing, staging and monitoring of lymphoma. Lymph nodes greater than 1 cm in diameter on an axial CT are considered positive [7]. Routine staging tests include CT of chest, abdomen and pelvis [7]. A thoracic CT scan reveals abnormalities in 7-30% of patients with initially normal chest x-ray and additional abnormalities in 25% with abnormal chest x-ray [8]. CT scan of abdomen and pelvis can show intra-abdominal or pelvic disease (Souhami & Tobias, 2003). No bone scan was performed. However, bone scan is indicated if musculoskeletal symptoms are present or alkaline phosphatase is elevated [9].

Imaging performed to assess treatment response

CT scan on completion of patient's chemotherapy showed a residual low volume mediastinal and pretracheal disease. The subsequent PET scan has shown this to be positive. The residual soft tissue mass did show some residual FDG activity and may therefore represent residual active tumour. There was also moderate focal activity seen at RT lung hilum and behind the medial right clavicle. PET scanning is a promising method for identifying patients that after initial treatment can or cannot be considered to be in complete remission [10]. NICE guidelines recommend use of FDG-PET-CT imaging for staging purposes in case of stage 1 DLBCL that is confirmed by clinical and CT criteria as well as in Stage 1 and II Localized follicular and Burkitt Lymphoma [11]. The recommendation to use FDG-PET-CT to confirm staging for patients diagnosed with other stages and/or subtypes of NHL, if it considered to alter oncological management of the disease.

Biopsy of the primary site

Biopsy of the primary lesion (mediastinal mass) was carried out to obtain histological diagnosis. Pathology report confirmed a diffuse large B-cell lymphoma. A definitive diagnosis is made only by biopsy of pathologic lymph node or tumour tissue [9]. Guidelines from NICE also recommend biopsy for the accurate diagnosis of Diffuse large B cell lymphomas. NICE further emphasis on use of excisional biopsy in most cases as it is a straight forward way to obtain correct diagnosis. In other cases, core needle biopsy can be carried out [11]. Johnson and Davies, advocate application of Mediastinoscopy in the diagnosis of PMBL that is localized to mediastinum without Lymph node involvement [12].

Bone marrow aspirate and trephine

Bone marrow aspirate and trephine biopsy was performed to determine bone marrow involvement. The result was negative. Bone marrow biopsy is a standard clinical investigation and a core of 15-20mm is considered adequate for histological evaluation [13]. A retrospective analysis of 192 patients with stage 1-11 diffuse large B-cell lymphoma showed a low (3.6%) overall incidence of bone marrow involvement [14].

Cerebrospinal fluid Cytology -CSF

CSF examination was not performed as PMBL is not associated with high risk of CNS involvement. CSF examination is indicated in diffuse aggressive NHL with bone marrow, epidural, testicular, paranasal sinus or nasopharyngeal involvement and primary CNS lymphoma [9]. Van Biesen recommended to check CSF with the help of flow cytometry and cytology if clinical features related to higher risk of CNS involvement exist [15]. These clinical features were not present in this case study. Hence no CSF test was carried out.'

Cell surface markers

The tumour was found to be CD20 positive which verifies its B-cell nature. PMBL is a B-Cell tumour and its B-cell phenotype can also be determined by CD20 positivity [6]. Dunleavy and Wilson listed Detailed history and Physical examination, evaluation of hematological and biochemical parameters, CT of chest, abdomen, pelvis and bone marrow Aspirate biopsy as part of diagnostic workup for Primary Mediastinal B-cell Lymphoma [16]. Echocardiogram may be carried out if the patient presents with pleural and pericardial effusions [16]. No written notes show that echocardiogram was performed in this case study but MUGA was done.

Staging

The patient was staged using Ann Arbour staging system and International Prognostic Index (IPI) for NHL as stage2A IPI 1/5. The current recommendation is to use both of these staging systems for the evaluation of a new patient diagnosed with NHL [13]. Stage 11 means involvement of 2 or more lymph node regions on the same side of the diaphragm – in this case study mediastinal and Hilar represent 2 lymph node regions. Absence of fever, night sweats or unexplained loss of $\geq 10\%$ of body weight is denoted by suffix letter A [17]. IPI system is used to categorize patients into risk groups and to predict on chances to achieve a remission, remain in remission and overall survival [13]. A score of 1/5 puts the patient in low risk group. In this case study the only adverse prognostic factor according to IPI is age $>$ than 60 years. According to the international non-Hodgkin's lymphoma prognostic factors project, the low risk group had an 87% complete remission and an overall survival –OS of 73% at 5 years versus a 44% complete remission rate and 26% survival at 5 years in the high-risk group [18].

Management of PMBL

Management of the stage 11A PMBL was based on the prognostic factors (age etc), stage (extent of disease) and histological subtype, which is an indication of aggressiveness and dissemination. Treatment modalities included chemotherapy, immunotherapy and External beam Radiotherapy (EBRT).

Chemotherapy

Patient received 6 cycles of Rituximab-CHOP-14 along GCSF support as first line treatment for management of intermediate grade DLBCL. Patient was placed in a then currently running Ph3 multicentre randomised clinical trial comparing Rituximab (R) with CHOP given every 14 days (6cycles of CHOP & 8 cycles of R) and Rituximab with CHOP given every 21 days (8 cycles of CHOP and Rituximab) for the treatment of patients with newly diagnosed diffuse Large B-cell NHL. The aim of this trial was to determine whether combination of Rituximab and CHOP-14 improve the survival in patients with DLBCL in comparison to those receiving

R-CHOP-21.

NHL tends to be less localized than Hodgkin's disease hence Chemotherapy has gained a more predominant role in its management over the past decade [19]. In patients with PMBL initial treatment is with anthracyclin containing regimen such as CHOP [5]. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) is a standard chemotherapy regimen for the treatment of DLBCL in low and intermediate prognostic groups [19].

Fisher and colleagues reported the results of a phase3 trial that compared CHOP with third generation chemotherapy regimens [20]. No significant differences were found between the treatment groups in terms of complete/partial response and survival. However combined grade 4 and 5 toxicities were lower in CHOP and Pro-MACE-CytaBOM group than MACOP-B and m-BACOD regimens. Hence CHOP remains the treatment of choice for intermediate/high grade NHL as this study and others have failed to demonstrate a convincing benefit of second or third generation chemotherapy regimens in the management of aggressive lymphoma.

There are two strategies employed for patients with stage 1-11 disease (without poor prognostic factors). One involves chemotherapy alone with a doxorubicin-containing regimen such as CHOP and the other involves a shortened course of chemotherapy followed by involved field Radiotherapy, IFRT [4]. There is no consensus on how many cycles of CHOP are needed in this setting. Patients with non-bulky ($<10\text{cm}$) disease can be treated with 3-4 cycles of CHOP followed by loco-regional radiation whereas patients with bulky disease ($>10\text{cm}$), including large mediastinal masses, probably benefit from 6-8 cycles of CHOP followed by radiotherapy [9]. Besien and colleagues state that all patients except those with small mediastinal masses ($<10\text{cm}$) and with stage1 should receive 6 cycles of chemotherapy in case of PMBL [6]. They further recommend the use of gallium scan and CT scan at the end of chemotherapy to determine response and subsequent risk of recurrence. This justifies the use of 6 cycle of CHOP (anthracycline based regimen) as initial treatment and a subsequent PET/CT scan at the completion of induction chemotherapy in this case study.

Immunotherapy

Patient received immunotherapy in the form of Rituximab. Rituximab is a monoclonal antibody against the CD20 B-cell antigen. It was given as an intravenous infusion of 375mg/m². A single arm phase2 study evaluated rituximab in combination with CHOP as first line treatment for aggressive NHL. Treatment was administered at 21 days intervals with Rituximab given on days 1 and 3 of each cycle at standard doses. Overall response rate was 94% with a complete response rate of 61% [21]. Coiffer and associates reported improved complete response rate and prolonged survival in elderly patients (> 60 years) with DLBCL when treated with Rituximab and CHOP without a clinically significant increase in toxicity [22]. This study reported a significant benefit

of the combined immunochemotherapy in both patients with low risk IPI and those with high risk IPI. The long-term results of the above study are quoted by Feugier and colleagues [23]. Almost half of R-CHOP patients are event free at 5 years compared with 28% in the CHOP arm. This shows superiority of R-CHOP over conventional CHOP and makes it the new standard for elderly patients with aggressive NHL. Rituximab can cause infusion-related reactions that require monitoring [24].

Growth Factors

G-CSF (granulocyte colony-stimulating factor) was prescribed to be given from days 4-12 in the form of Lenograstim to deal with neutropenia. G-CSF is a myeloid growth factor for the production of functionally active neutrophils and is approved for clinical use to reduce the incidence of febrile neutropenia in cancer patients receiving myelosuppressive chemotherapy or to stimulate neutrophil recovery following high dose chemotherapy with stem cell support [25]. The most common side effect observed with the use of G-CSF is mild to moderate bone pain [25]. The successful use of G-CSF to support recovery of granulocytes in 2-week regimens has already been reported by NHL-B trial of German High-grade Non-Hodgkin's Lymphoma study Group-DSHNHL [26].

Consolidation Radiotherapy

On completion of chemotherapy, patient had a CT and PET scan which showed residual tumour as mentioned earlier. In the absence of complete metabolic response to R-CHOP treatment, Patient received consolidation radiotherapy to the mediastinum and right neck in order to treat residual tumour and to reduce recurrence. Most PET-positive patients at the end of the induction treatment relapse within the first 2 years [27]. This was an indication that some sort of consolidation therapy was required to reduce risk of recurrence in the patient as his both post chemotherapy PET and CT scans were positive. Besien and colleagues recommended consolidation therapy with radiation or high dose chemotherapy if the gallium scan/CT scan remains positive or a significant residual mass is present at the completion of the treatment of PMBL as it increases the risk of recurrence [6]. In the absence of prospective data comparing these approaches both options could be appropriate. At author's centre consolidation with radiotherapy is recommended. A retrospective review of 40 patients with stage 1 or 11 PMBL treated with CMT (combined Modality therapy) showed excellent loco-regional control and lack of significant toxicity in patients who received Doxorubicin based chemotherapy followed by consolidate radiotherapy [28]. A retrospective Japanese study showed that patients with positive PET at the end of R-CHOP had better O.S. (100 vs.60 %) and PFS (80 vs.17 %) at 4 years when given RT than those who did not get RT [29]. This study concluded that combined Rituximab and Chemotherapy improves outcomes of patients with PMBL and PET could forecast the need for RT in these patients. These findings support the management strategy

employed in the present case study.

Radiotherapy Prescription

Patient received a total dose of 35Gy in 20 fractions at mid plane dose with 6 MV photon energy as EBRT. Variations of doses exist among clinicians. Most patients with intermediate grade lymphomas who are treated with CHOP and followed with Involved field RT-IFRT can be prescribed 30-35Gy who has responded to chemotherapy [17]. Otherwise doses of 40-50Gy are used in intermediate grade lymphomas including Diffuse large B-cell lymphoma.

Localization

The radiotherapy treatment was CT planned. Anterior-posterior (AP) fields were drawn on the simulator film after assessing pre and post chemotherapy CT scans. Lee and colleagues state a similar CT based radiotherapy plan for lymphoma treatment using AP fields drawn on simulator films after assessing pre and post chemotherapy CT scans with an addition of 5mm margin on the inferior border of the disease [7]. They further reported usefulness of the FDG-PET scan in the RT planning of thoracic lymphoma patients resulting in better determination of lung blocks and field.

Position

Patient was treated in supine position with chin extended with a chin strap. Bomford and Kunkler propose that for a mantle field patient lies supine with chin extended to exclude as much of oral cavity as possible [2].

Radiotherapy volume and field arrangements

A modified mantle field was used to deliver radiotherapy to mediastinum and Right neck using an AP field. The field covered the mediastinum, supraclavicular regions and RT neck. All prechemotherapy volume was covered by the radiation field. Similar treatment volume (mediastinum and supraclavicular region) with modified mantle field is shown to be appropriate for stage 1 and 11 PMBL with only 3% marginal failure [28]. Chao and colleagues stated that for patients involving right upper cervical nodes, the irradiation volume includes the entire right neck and supraclavicular fossa [17]. Due to advances in radiation oncology technologies, IMRT can also be used to treat PMBL these days.

Field borders

In superior-inferior direction the fields extended from tips of mastoids to the bottom of T10 thoracic vertebrae and lateral border followed inside of rib cage with approximately ½ cm lung showing laterally or lower border of 4th rib. Bomford and Kunkler stated similar field arrangement and borders, setting upper limit of the field on a line joining the chin to the external occipital protuberance thereby including the occipital, submental and subaxillary nodes in

the volume [2].

Shielding

Multi leaf collimators were used to protect the lung. Lung is shielded lateral to the mediastinum along the lower border of the 4th rib posteriorly [2].

Radiotherapy side effects

The patient suffered from grade1 skin reaction and mild oesophagitis which were managed with 1% hydrocortisone cream and soluble paracetamol as recommended by [30]. Late side effects may include radiation induced pneumonitis, pericarditis, injury to spinal cord, hypothyroidism and increased risk of secondary cancers. With respect to radiotherapy lowering of blood count may occur thus increasing the risk of infection, anaemia and bleeding. Therefore, blood test needs to be performed during radiotherapy treatment to monitor blood count. Moreover, mediastinal irradiation increases the risk of cardiac toxicity especially when given after anthracycline chemotherapy.

Chemotherapy side effects and professional implications

Chemotherapy side effects can be divided into 4 categories by time of occurrence namely immediate, early, delayed and late onset of toxicity [31]. One of the most common immediate side effects of chemotherapy drugs is nausea and vomiting [31]. The emetic potential of cyclophosphamide, doxorubicin and vincristine range from 50-25% and high dose cyclophosphamide carry an emetic potential > 80% [31]. These are managed by antiemetics. When designing antiemetic treatment one of the professional implications is to make sure that antiemetics must have duration of action for the period of expected nausea and vomiting from specific chemotherapy agents. In this case study metoclopramide 10mg tds were given 30-40 min prior to treatment. Early side effects of CHOP include Neutropenia and thrombocytopenia as a result of bone marrow depression as reported by a number of studies [32-33]. Neutropenia is prevented and managed by use of G-CSF as discussed above. Thrombocytopenia is a decrease in platelet count of less than 100,000/mm³ and is associated with increased risk of bleeding [31]. Platelet transfusion is required if there are signs or symptoms of bleeding or if platelet count is < 20,000/mm³. As patient was already on Warfarin for previous DVT, this should be discontinued in case of thrombocytopenia.

Professional implications include monitoring of patients absolute neutrophil and platelet count before administration of each chemotherapy cycle. Other professional implications include nursing interventions aimed at prevention of infection by maintaining intact skin and mucous membranes and minimizing exposure to environmental sources of infection as well as early diagnosis and intervention if infection occurs. Initial patient education was given before chemotherapy to prepare the patient

for self-care especially from protection from infection and injury and self-assessment.

Doxorubicin causes alopecia in > 80% of patients treated usually within 21 days [31]. This case study patient also suffered from alopecia. Patient was advised about hair loss and various measures to take during hair loss such as wigs and scarves. Patient received advice on proper scalp care such as use of mild soap, soft brushing, and use of sunscreen when exposed to sun.

Delayed reactions involve peripheral neuropathy (Vincristine). Doxorubicin also has cardiotoxicity and the patients need to be monitored for any cardiac changes. Professional implications include echocardiogram and subsequent radionuclide ventriculogram (MUGA scan) to monitor cardiac function and identify chemotherapy induced injury [34]. This patient also had a MUGA scan prior to and during chemotherapy. Late effects of CHOP chemotherapy may include second malignancies such as bladder cancer (cyclophosphamide).

Discussion

British society for Haematology recommends carrying out base line PET-CT scan in all patients at the time of diagnosis and bone marrow biopsy is not required if PET-CT scan is already performed [35]. BM biopsy is indicated if it can change risk management e.g. if a patient presents with extra-nodal disease there is a risk of CNS involvement and BM can confirm lymphomatous infiltration leading to CNS prophylaxis. These guidelines further recommend carrying out core or excisional biopsy to obtain histological diagnosis.

The study by Khan and colleagues concluded that PET-CT was highly accurate for diagnosing Bone marrow involvement in DLBCL with sensitivity and specificity of 94% and 100% compared to 40 and 100% for marrow biopsy [36]. PET diagnosed all clinically relevant marrow involvement and biopsy did not upstage any patient. PET positive marrow involvement is unlikely to show clinically significant marrow involvement identified by biopsy. Similarly, cases with limited focal deposits far from iliac crest are unlikely to gain from biopsy. Authors of the study however suggested use of iliac crest biopsy in case of increased FDG uptake throughout skeletal marrow to eliminate other pathologies e.g. myelopoiesis.

The patient in the present case study showed no bone marrow involvement after having Bone marrow aspirate and trephine biopsy as mentioned earlier. There is good evidence that in many cases BM involvement can be accurately determined by PET-CT without employing invasive procedures like Bone marrow aspirate and trephine biopsy. In certain cases, Bone marrow biopsy is still carried out to determine that the increased metabolic activity seen on PET-CT is actually due to PMBL and not by some other disease or pathology and /or when it can affect risk management. The diagnostic work up in the present case study differs from

latest guidelines in terms of absence of baseline PET-CT scan and inclusion of BM biopsy.

Imaging working group recommends optimal use of PET-CT in staging and response assessment of lymphomas [37]. Interim PET is often employed in clinical practice to assess the efficacy of treatment and to eliminate the presence of disease progression. Various studies have indicated that interim PET is a powerful prognostic indicator in HL and aggressive NHL [37]. Thus, interim PET can be used to customize treatment but there is no definitive conclusion that it will affect the outcome [38, 39]. Hence the working group recommended use of interim PET to assess early response because it is better than CT alone and only alter treatment based on interim PET-CT findings if there is strong evidence of progression [37]. In the present case study, a CT scan followed by a PET scan was performed after completion of R-CHOP to assess treatment response. Not sure if it can be classified as interim PET as generally interim PET scan is carried out after 2nd cycle of chemotherapy. Furthermore, a positive FDG PET-CT is associated with poor OS, PFS and EFS [11]. The PET scan after completion of R-CHOP induction chemotherapy seems to fall under the category of end of Chemotherapy treatment PET scan and it provided adequate response assessment required to see presence of complete or partial remission (for remission assessment). This in turn dictated second stage of treatment. Due to the presence of residual disease seen on PET scan, consolidation RT was given to mediastinum and right neck to treat residual disease and to reduce the risk of recurrence. A study by Martelli and colleagues, showed that PET-CT after Rituximab and anthracycline containing chemotherapy, defines the role of Radiotherapy in patients with PMBL the PFS at 5 years was superior in PMBL patients showing Complete metabolic remission than patients with residual metabolic tumour activity [40].

Studies have shown that functional Parameters of baseline PET-CT scan have prognostic values in the management of PMBL. A prospective study by Ceriani and colleagues indicated that metabolic heterogeneity (MH) seen in baseline PET scan of PMBL patients could be an indicator of chemoresistance in solid tumours [41]. This means in these patients first line chemotherapy is likely to fail. PFS at five year was 94% in low MH group compared to 73% in high MH group. More over cox analysis of PFS indicated that two PET functional parameters namely Total lesion glycolysis and MH are associated with high risk of disease progression. Thus, TLG and MH are prognostic tools in assessment of PMBL outcomes.

Another study using the same set of patients as mentioned above, Ceriani and associates showed that In univariate analysis, metabolic tumour volume and Total lesion glycolysis were significantly related to inferior PFS and O.S. where as in multivariate analysis only TLG showed significantly inferior overall survival and progression free survival (O.S. was 100% for low TLG and 80% for high TLG and PFS was 99% for low TLG vs. 64% for high TLG at 5 years) [42]. Authors

concluded that TLG is a strong prognostic factor for PMBL outcomes and needs further validation as a biomarker. These studies show that baseline PET-CT has a significant role in the management of PMBL and are useful in predicting PFS and OS and a base line PET-CT scan should be performed. The present analysis also favours use of interim and End of combined modality Treatment PET-CT scan and their comparison with baseline PET-CT scan to better monitor treatment response and to justify any consolidation treatment.

In terms of response assessment, the good practice guidelines from British Society for Haematology good practice paper recommended patients should have a PET-CT scan post combined modality treatment (R-CHOP + ISRT- patients outside clinical trial) whereas patients treated with DA-EPOCH-R should have a PET-CT scan 6 weeks post chemotherapy [35]. Despite lack of prospective studies there is good evidence from various retrospective and a prospective study that addition of Rituximab to CHOP, MACOP-B and to an intensive chemotherapy regime DA-EPOCH is an effective treatment for PMBL patients with good prognosis [43, 44]. Addition of Rituximab to CHOP and MACOP-B followed by mediastinal RT resulted in 5-year PFS of 75-85% where as more intensive chemotherapy regime (DA-EPOCH-R) showed encouraging results [43]. This study further concluded that PET-CT is good for defining treatment response. Reduced progressive disease (2.5%) and Improved 3-year event free survival (78%) were reported by Mabthera International prospective trial in young PMBL patients (IPI=0-1, better risked) when Rituximab was added to 6 cycles of CHOP [44]. A sub group analysis of UK NCRI PH 3 randomized trial of R-CHOP14 vs. R-CHOP 21 involving stage 1 and 11 PMBL patients with median age 38.5 years showed better overall and PFS for patients in R-CHOP 14 arm vs. R-CHOP 21 [45]. However, the difference was not statistically significant ($p=0.06$ for O.S. and $p=0.10$ for PFS). Patients in CHOP 21 experienced more events as well. (Please note generally P equal to or less than 0.05 is considered significant). O.S. and PFS at 5 years for all patients were 83.3% and 79.8%. Although Intensive and complex Radiotherapy free chemotherapy regimens like DA-EPOCH-R seem to provide good EFS, OS and complete remission rates this data needs to be verified in randomized multicentre ph3 trials. DA-EPOCH-R was associated with more toxicity and showed no difference in outcome compared to R-CHOP plus ISRT in a prospective randomized trial [46]. Guidelines from European society for medical oncology recommend use of R-CHOP 21, R-CHOP 14, R-VACOP-B, V-MACOP-B, and DA-EPOCH-R as choices for 1st line therapy for PMBL patients whereas guidelines from US National comprehensive Network (NCCN) advocate either R-EPOCH or R-CHOP as initial therapy [47, 48].

All these studies clearly show that addition of Rituximab to CHOP and CHOP like regimens followed by RT tends to improve treatment outcomes. There is not enough evidence to suggest that omitting RT even in case of complete metabolic response after R-CHOP is warranted. There is still risk of locally progressive

disease and recurrence. Anthracycline based Chemotherapy followed by RT is likely to improve patient outcome in case of both partial and complete remission. The present literature review recommends that DA-EPOCH-R should only be considered if RT cannot be given or when short- and long-term high toxicity from Chemotherapy can be well tolerated and managed which is not easy to achieve and not always possible. Complex Chemotherapy regimens should be given in centres experienced in giving complex Chemotherapy. There are no studies that compare the R-CHOP and DA-EPOCH-R in randomized controlled trial in PMBL patients therefore the present analysis favours use of R-CHOP and ISRT in PMBL patients. Therefore, for the time being it is safe to say that R-CHOP or CHOP-like regimes followed by consolidative RT remain the 1st line standard treatment of choice for PMBL patients.

Conclusion

Treatment of PMBL has evolved over the years. Combined modality treatment in the form of anthracycline-containing chemotherapy followed by mediastinal irradiation is treatment of choice for stage 1a PMBL. Addition of Rituximab improves response rate and overall survival. GCSF support reduces myelotoxicity and treatment time. PET-CT can also be used instead of Bone marrow aspirate to correctly indicate bone marrow involvement. It is recommended to use Baseline PET-CT scan and interim and end of combined modality treatment PET-CT scan. Professional implications include appropriate use of antiemetics, monitoring of blood counts as well as cardiac function and patient education to prepare him/her for self-care.

Funding

No funding or financial support was taken to carry out the case study.

Conflict of Interest

Author declares no conflict of interest

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