Malays J Pathol 2023; 45(1) : 1 – 10

REVIEW ARTICLE

Diffuse large B-cell lymphoma research in Malaysia: A review

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Abstract

Lymphomas are prevalent worldwide and a common malignancy reported in Malaysia. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of B-cell lymphomas accounting for 54% to 65% of all B-cell lymphomas and 39% to 57% of all malignant lymphomas. However, DLBCL comprises a heterogeneous group of diseases with different clinical presentations, biology and response to treatment. Recent advances in understanding the genetic landscape and molecular features of DLBCL have identified high-risk subsets with poor outcomes to chemo-immunotherapy that are actively being studied in various clinical trials. C-MYC is a proto-oncogene located in chromosome 8q24. 10 to 15 % of patients with newly diagnosed DLBCL have an underlying rearrangement of the MYC oncogene, resulting in dysregulated cellular survival and proliferation. Approximately half of these cases also carry a rearrangement of the anti-apoptotic proto-oncogene BCL2 and/or its transcription repressor BCL6. Over 20 case reports of DLBCL cases with notable features in Malaysia have found in the literature, in addition to a few extensive case series and included in this review. R-CHOP remains the mainstay of therapy and can help achieve control of long-term disease in nearly 90% of patients presenting with limited-stage and in up to 60% of those presenting with advanced stages. This review captures all 52 studies that reported DLBCL in Malaysia and summarises the essential aspects, including prevalence, subtype, prognostic markers clinical features in presentation and limited outcomes of cases when available.

Keywords: DLBCL, Lymphoma, Review, Malaysia

INTRODUCTION

Lymphoma or malignant lymphoma is a diverse group of malignant proliferations that arise as discrete tissue masses. Worldwide, the prevalence of malignant lymphomas ranges from 5% to 6% of all malignancies.[1] They are the fourth most frequent type of neoplasms in Malaysia, with 5.2%, in males is 6.6%, and in females is 3.8%.[2]

The World Health Organization (WHO) established the detailed classification of lymphomas, with the most recent published in 2016.[3] Mature B-cell neoplasms are classified into follicular lymphoma; Diffuse large B-cell lymphoma (DLBCL), T-cell/histiocyte-rich large B-cell lymphoma; Primary mediastinal (thymic) large B-cell lymphoma; Burkitt lymphoma; Burkitt-like lymphoma with 11q aberration; High-grade B-cell lymphoma.

DLBCL, as its name indicates, is based morphologically on the microscopic appearance of large B-cells seen diffusely throughout the lymphoma. It is a heterogeneous group of tumours with aggressive classic high-grade lymphoma features. It is the most prevalent type of NHL, accounting for 30–40% of all lymphomas.[4]

MATERIALS AND METHODS

A search was conducted on the following: (1) bibliographic databases (PubMed and Scopus,); (2) Individual journal search of Malaysian health-related journals; (3) A targeted search of Google and Google Scholar; (4) Searching of Malaysian institutional repositories; (5) Searching of Ministry of Health and Clinical Research Centre website. The citations were manually entered or imported into the bibliographic software RefWorks.

The search terms used were Malaysia AND lymphoma, and information in this report is

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extracted from a more comprehensive library of published data that covered all lymphomas. The review of other lymphomas will be published separately. The search was performed on 18 May 2021, and repeated on 3 July 2022.

RESULTS

The search earmarked a total of 451 papers in the first search. An additional 65 papers were noted on 3 July 2022. A number that was not related to lymphoma or findings in Malaysia were excluded. Four authors (LKG, SPV, AFS & IAS) carefully examined all 516 papers and deleted unrelated papers. The final number of papers used in this study was 52.

SECTION 1: REVIEW OF LITERATURE

Case series in Malaysia have reported that DLBCL account for 54% to 65% of all B-cell lymphomas and 39% to 57% of all malignant lymphomas.[5-7]Ting *et al*. found that of 120 DLBCL cases, 43.3% were nodal, 14.2% from the Waldeyer's ring, and the remaining 42.5% were extranodal.[7] In the largest series of 141 cases of DLBCL seen between 2004 and 2010 from UKM, Phang *et al*. found that 79 (56%) were male and 62 (44%) females. They ranged from 5 to 84 years, with a mean age of 60. There were 77(55%) Malays, 55(39%) Chinese, 2(1.4%) Indians, and 7(5%) of other races. Lymphoma was nodal in 59 (42%) and extranodal in 82 (58%) cases.[8]

Classification of DLBCL and their prognostic significance

To better manage such a heterogeneous group of malignancies as DLBCL, that are often aggressive, it is imperative to understand how subtypes differ and identify markers that relate to prognosis. Classification can better target treatment and know what outcome to expect. It is also useful to discuss survival outcomes related to these markers rather than in a section about management separately.

Germinal centre B-cell (GCB) and non-GCB subtypes

DLBCL can be broadly divided into two large prognostic groups: germinal centre B-cell subtype (GCB), which has a better prognosis, and non-GCB, which includes activated B-cell (ABC)-DLBCL. Classification can be achieved by both gene studies and their protein expression.

From the 79 patients from Universiti

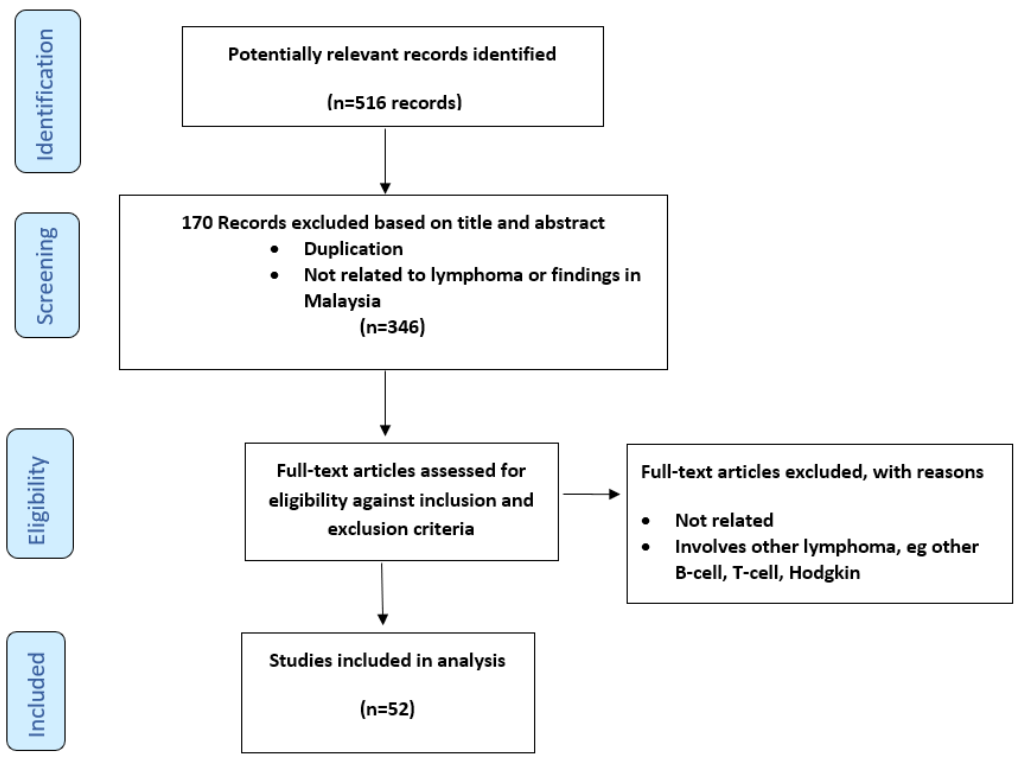

FIG. 1. PRISMA diagram of workflow.

Kebangsaan Malaysia (UKM) with DLBCL (nodal, 59% and extranodal, 41%), Masir *et al*. found 39 (49%) were activated B-cell (ABC)-DLBCL, 29 (37%) GCB-DLBCL and 11 were unclassified (U/C)-DLBCL, using the Lymph2Cx assay to quantify gene expression.[9] Their aim included assessing the expression pattern of various signalling molecules of the B-cell receptor (BCR) and Toll-like receptor (TLR) pathways, in particular Bruton's tyrosine kinase (*BTK*) and *LYN* (an Src family tyrosine kinase) genes. All patients were immune-competent and received standardised clinical management, including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) ±bone marrow transplant at a tertiary care cancer hospital in Kuala Lumpur, Malaysia. They confirmed that ABC-CLCBL had an inferior overall survival, finding a median overall survival of 19 months for GCB-DLBCL compared with 11 months in ABC-DLBCL and 11 months in U/C-DLBCL. In ABC-DLBCL, *BTK* expression exerted poor response to R-CHOP, while overall survival in ABC-DLBCL with low *BTK* expression was similar to the GCB-DLBCL subtype. High *LYN* expression and poor overall survival for ABC-DLBCL and GCB-DLBCL subtypes. Furthermore, high co-expression of (*BTK*)/*LYN* (*BTK* high/*LYN* high) showed poor survival.[10]

It is expensive and impractical to perform microarray gene analysis on every patient with DLBCL. With that in mind, Hans (2004)[11] and Choi (2009)[12] have created widely used algorithms to match protein expression to these GCB and non-GCB subtypes. Hans used CD10, BCL6, MUM1, BCL2, and cyclin D2, while Choi used GCET1, CD10, BCL6, MUM1, and FOXP1. From the Malaysian studies, the proportion of GCB-DLBCL appears to be lower than in Western countries and comparable to Korea, China, and Taiwan.[8] An early series of patients from 1996-2003 at Universiti Malaya found that 33/84 (39.3%) had the GCB phenotype, and the remainder (60.7%) had the non-GCB phenotype.[13] Forty-five patients had complete clinical follow-up data. Only three patients received rituximab. Patients with GCB phenotype did not have a better prognosis, and BCL-2 expression was not associated with a better prognosis. The expression of BCL-6 was associated with a lower overall survival rate.

Using the Hans algorithm in a series of 32 cases of specifically extranodal upper aerodigestive tract DLBCL, Wong *et al*. found that 34% (11/32) were germinal centre B-cell-like (GCB), and 66% (21/32) were non-GCB types; 59% (19/32) had combined patterns A and B, and 41% (13/32) had the pattern C. EBV-encoded small RNA (EBER) *in situ* hybridisation stain demonstrated only one EBV infected case.[14]

Retrospectively, studying 29 cases with sufficient clinical data in Kelantan, using the Hans algorithm, Wan Najmiyah *et al*. categorised 34.5% as GCB-DLBCL, and the rest were classified as non-GCB.[15]

Ting *et al*. in a retrospective study of diagnostic tissue samples of DLBCL patients between 2012 to 2013 from four major hospitals in Malaysia, found using the Hans algorithm on 120 cases that 74.2% were non-GCB, whereas 25.8% were GCB.[7] Their mean follow-up period was 25 months. They found no significant correlation between GCB/non-GCB DLBCL subtypes, age of diagnosis, gender, international prognostic indices (IPI) scores, disease stage, and serum lactate dehydrogenase level (LDH), and the 2-year survival rate. They found an overall survival at two years was 73% (47/64) for the R-CHOP-like regime compared to 44% (15/34) with the CHOP-like regime. The survival was 66% (12/18 for R-CHOP-like) and 28% (2/7 for CHOP-like) for GCB-DLBCL and 76% (35/46 for R-CHOP-like) and 45% (12/27 for CHOP-like) non-GCB-DLBCL.

In the UKM series of 141 cases, 32.7% were GCL-DLBCL, and 67.3% were non-GCB using the Hans algorithm. 72% presented in late stages (Ann Arbor III & IV). A 4-year survival was 48.5% for GCL-DLBCL and 10.5% for non-GCL-DLBCL ($p=0.01$). Two-year survival was 60.6% and 23.6%, respectively. The presence of B symptoms, such as loss of weight, night sweats, fever, elevated serum LDH, and age above 60 years, were also significant for poor prognosis.[8]

Double protein expression lymphoma (DPL) and Triple protein expression lymphoma (TPL)

DPL and TPL, or 'Double/Triple-hit' lymphoma involving gene rearrangement and protein expression of MYC and BCL2/BCL6 are also commonly used terms to describe the poor prognostic types of DLBCL.

Wan Najmiyah *et al*. found that MYC, BCL2, and BCL6 proteins were expressed in 72.4%, 62.1%, and 62.1% of DLBCL patients, respectively. Concurrent expression (c-MYC/BCL2 and/or BCL6 positive) was present in 58.6% of patients. DPL and TPL were significantly associated with elevated LDH

level (*p=0.018*), IPI score (*p=0.003*), Ann Arbor stage (*p=0.011*) and complete response rate (*p=0.011*).[15] Phang *et al*. found no significant difference in survival in the dual expression of MYC/BCL2 genes (*P=0.916*). Fluorescent *in-situ* hybridisation (FISH) analysis found there were 9.22% (13/141) gene rearrangement cases; the commonest were BCL6 (10), followed by MYC (2) and BCL2 (1). There were no BCL10 and MALT-1 gene rearrangements detected. More cases of MYC protein overexpression were observed compared to *MYC* translocation.[8] Ting *et al*. found that in their series, 13.3% of patients had DPL, and 40% had TPL. c-*MYC*, *BCL2,* and *BCL6* gene rearrangements were 5.8%, 5.8%, and 14.2%, respectively; on FISH analysis and 1.6% were Double Hit Lymphoma (DHL). They reported lower median overall survival (*p<0.05*) in patients with EBER positivity, DPL, TPL, c-*MYC* gene rearrangement, *BCL2* gene rearrangement, extra copies of the *BCL2* gene, and *BCL6* gene rearrangements. IPI score was the important determinant of median overall survival in DPL and TPL (*p<0.05*). *c-MYC*, *BCL2*, and *BCL6* gene rearrangements showed a weak correlation with the expression of MYC, BCL2, and BCL6 proteins. They concluded that FISH analysis is the preferred technique for the prediction of treatment outcomes in DLBCL patients.[7]

In a retrospective study of 104 patients between 2012 and 2015, Teoh *et al*. found patients with high International Prognostic Index (IPI) (score 3-5) and co-expression of c-MYC/BCL2 protein had significantly poorer overall survival and event-free survival, respectively (P<0.05). c-MYC/BCL2 protein co-expression was more common in non-GCB-DLBCL (P=0.048) and contributed to adverse prognosis in this group of patients.[16]

CD5 protein expression

Phang *et al*. noted that 12% (11/92) of their series were CD-5 positive and cyclin D1 negative, excluding mantle cell lymphoma. There were no significant differences in patient characteristics among this 12% compared to other DLBCL cases. 90/9% (10/11) of them were non-GCB. They showed a significantly poorer outcome with treatment regardless of rituximab. Nine died of the disease.[8] Ting *et al*. had 8/120 (6.7%) of their DLBCL patients positive for CD5. Most of these patients had high IPI scores and advanced disease. These patients received different treatment regimens but fared worse than CD5 negative patients on the same regime.[7]

Other Prognostic Markers

In addition to the genes mentioned above, DLBCL is associated with many immunohistochemical markers, including CD19, CD20, CD22, CD75, CD79a, PAX5, CD30, IgM>IgG>IgA, CD10, MUM1, Ki67, OCT-2, BOB1, GCET1, c-MYC, FOXP1, and LMO2.

The pattern of CD15, CD30, and BCL-2 expression in DLBCL at the University Malaya was investigated in 67 consecutive cases (M: F=1.2:1) with a median age of 55 years using immunohistochemistry on paraffin-embedded tissue. Nodal expression was more common than extranodal in presentation. Only 3 of the 67 cases expressed CD15. In addition, 3 cases showed weak membrane staining for CD30; however, only one case had co-expression of CD15, and a few tumour cells showed weak expression of CD30. Bcl-2 protein was expressed in 43 of 67 (64%), more frequently in nodal than extranodal tumours.[17]

The FOXP1 oncogene is a prognostic marker that shares partially overlapping regular tissue expression and functionality with FOXP2. FOXP2 expression is mainly seen in multiple myeloma, but a study from Kelantan, Malaysia, has observed FOXP2 expression in DLBCL patients who showed a lower immune response. However, the role of FOXP1 and FOXP2 in the immune response during the pathogenesis of high-risk DLBCL needs to be explored.[18] Wong *et al*. in their study, noted that in biopsies from DLBCL patients treated with immunochemotherapy (R-CHOP), FOXP2-positive diffuse large B-cell lymphomas exhibited a poor response to R-CHOP therapy with distinct biological signatures.[18]

In the pathogenesis of DLBCL, epigenetic mechanisms such as the methylation of *p16* have been reported as a contributing factors. In one study, researchers reported *p16* methylation in 65 of 88 (74%) samples, with a significant association observed between *p16* methylation status and patients aged >50 years old (*p=0.04*).[19] Lee *et al*. examined P16 protein overexpression in 70 cases of DLBCL. Using immunohistochemistry P16 overexpression was shown in 45.7% (32/70) of the DLBCL cases and was significantly correlated with CD10 (p = 0.022) and germinal centre B-cell-like (GCB) phenotype (p = 0.022). High expression of P16 was inversely associated with high proliferative activity (Ki-67 index greater than 75%) (p = 0.020). Of the 47 cases that yielded interpretable FISH results, 57.4% (27/47) showed deletions of *p16,* and 27.7% (13/47) showed gains of *p16*. P16

overexpression and *p16* deletions were mutually exclusive (p = 0.019). There was no correlation between P16 overexpression and *p16* gains (p = 0.621).[20]

DNA (cytosine-5)-methyltransferase 1 (DNMT1) is a maintenance enzyme involved in DNA methylation by adding methyl groups to DNA building blocks. Loo *et al*. found that DNMT1 was expressed in the very large majority of DLBCL cases, both GCB-DLBCL (109/118, 92.3%) and non-GCB-DLBCL (100/112, 89.2%) subtypes, but samples were from patients in Malaysia as well as other counties. Low and negative DNMT1 expression (20% cut-off) was predictive of worse overall survival and progression-free survival. Moreover, DNMT1 was frequently expressed in mitotic cells and significantly correlated with Ki-67 or BCL6 expression (r = 0.60 or 0.44, respectively; p < 0.001).[21]

Ting *et al*. noted that Ebstein Barr virus encoded RNA (EBER) was detected in 8 (6.7%) of their 120 cases with no difference between GCB and non-GCB subtypes.[7]

A private hospital in Kuala Lumpur studied 51 paraffin-embedded tissue samples of DLBCL. Ten EBV (+)-DLBCL cases were analysed further using immunohistochemistry for LMP1, pJAK1, pSTAT3 and MYC; FISH assay for *c-MYC* gene rearrangement to detect the EBV expression. The results showed that 90% were non-GCB subtype (*p=0.011*), 88.9% expressed LMP1, and 40% had *pJAK1* expression.[22]

STAGE OF DISEASE

Phang *et al*. in the series of 141 cases from UKM, noted most were diagnosed late; 29 (25.9%) were stage III, and 52 (46.4%) were in stage IV disease. Only16 (14.3%) and 15 (13.4%) were in stages I and II of the Ann Arbor staging, respectively.[8]

Bone marrow biopsy is the standard investigation for detecting bone marrow involvement in patients newly diagnosed with DLBCL. Siti Maisarah *et al*. investigated the role of 18F-FDG PET/CT for detecting bone marrow involvement in 21 DLBCL patients at Hospital Pulau Pinang. They reported the sensitivity and specificity of 18F-FDG PET/CT scans for detecting BMI to be 100% and 77.8%, respectively.[23]

CLINICAL FEATURES

Waldeyer's ring

Teh *et al*. reported a case of a 33-year-old Malay woman with a lump at the base of the tongue, which proved to be DLBCL on biopsy.[24] Chenthilnathan *et al*. reported another similar case.[25] They both achieved remission with R-CHOP chemotherapy. In the upper airway, nasopharyngeal DLBCL may cause airway obstruction, which may be of special concern in the covid pandemic.[26]

Face

Venkateswaran *et al*. reported DLBCL in the nasal passage not involving the nasopharynx in a 37-year-old male patient.[27] In a 66-year-old man with a swelling of the cheek, maxillary sinus DLBCL was diagnosed and trested with R-CHOP. Unfortunately the disease was not responsive to treatment and the patient succumbed a short time after the 4th cycle.[28]

Thyroid

Primary thyroid lymphoma is rare and accounts for less than 5% of thyroid malignancies. It is an aggressive disease with poor outcomes. Most thyroid lymphomas are non-Hodgkin lymphomas of B cell origin. Azlin *et al*. reported two cases of primary thyroid lymphoma from HUKM in 2010. In both cases, a 65-year-old Chinese man and a 68-year-old Malay woman presented with obstructive respiratory symptoms that required emergency surgical intervention. Both were diagnosed with DLBCL. The man received eight cycles of the combination chemotherapy (rituximab combined with CHOP) after surgery and survived for 12 months at reporting. The woman had concomitant thrombosis, initially involving the left internal jugular vein, which developed into a left subclavian and axillary thrombosis postoperatively, followed by pulmonary embolism sepsis and possibly another thrombosis within her coronary vessels. Eventually, she succumbed to the disease.[29] Yahaya *et al*. in HUSM Kelantan reported a case of a 69-year-old man who presented with Hashimoto's thyroiditis. He had minimal clinical features of thyrotoxicosis despite having markedly elevated serum free thyroxine and a rapidly increasing goitre. A surgery revealed a locally invasive tumour, DLBCL, besides Hashimoto's disease. He, too, succumbed on the seventh postoperative day due to coronary disease.[30]

Parotid

Primary malignant lymphomas of the salivary glands are rare, accounting for 2-5% of salivary

gland tumours. Almothafar *et al*. reported the case of a 66-year-old woman in Kota Kinabalu with rheumatoid arthritis, hypertension, and osteoporosis who presented with a swelling in the left parotid area for one week. A core biopsy of the parotid tumour revealed DLBCL. MRI revealed tumour infiltration involving the intramedullary, intradural, intramuscular, and vertebral bodies of T2 to T8 vertebrae. Radiotherapy was initiated to salvage her spinal cord compression, followed by the first cycle of chemotherapy. However, after the second cycle of chemotherapy, the patient suffered attacks of neutropenia, sepsis, and pneumonia and needed potent antibiotics, and further radical treatment was stopped. She died from disseminated disease one month later.[31]

Uterus

DLBCL has also been noted solely in the uterine cervix in a 43-year-old woman.[32]

Spleen

Kaniappan *et al*. reported a 40-year-old man who presented with acute pain in the left hypochondrium associated with abdominal distention. There was no history of preceding trauma or fever. On examination, he had tachycardia, pallor, and splenomegaly. Imaging studies showed collections in the spleen suggestive of splenic rupture and hematoma. Emergency splenectomy was done, and the splenic biopsy report was consistent with the diagnosis of DLBCL. The patient defaulted from chemotherapy.[33]

Kidneys

Mustafar *et al*. reported primary CD20 positive renal DLBCL in HIV patients with oliguric acute renal failure and large ballotable kidneys.[34]

Brain

Tee *et al*. reported primary DLBCL presenting in the basal ganglia and cerebral peduncle of the brain in a 61-year-old woman. She was treated with chemotherapy but died of neutropenic sepsis after the fourth cycle of chemotherapy.[35] A 48-year-old Chinese woman who presented with seizures, forgetfulness, and motor problems was found to have intravascular DLBCL in the brain. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) showed diffuse multiple asymmetrical hyperintense white matter lesions on T2 weighted and FLAIR sequences on MR imaging which were biopsied under image guidance. The patient recovered neurologically and was well two years after diagnosis following chemotherapy.[36] Another patient with high-grade suprasellar DLBCL, mistaken for tuberculosis, succumbed when the diagnosis was finally made four months after the presentation.[37]

Skin

Shamsudin and Chang reported the case of DLBCL in a 56--year-old Malay woman with extensive skin involvement.[38]

Other unusual presentations

A 39-year-old woman was found to have an anterior mediastinal mass. A CT-guided biopsy found chronic granulomatous inflammation suggestive of tuberculosis. After two months of anti-tuberculous treatment and no improvement, another CT-guided biopsy revealed DLBCL. The first tissue sample included noncaseating granulomas engulfing tumour cells and massive aberrant lymphoid cells that were CD20 positive and had a high Ki-67 proliferative index on histopathological review. She responded well to lymphoma chemotherapy (R-EPOCH).[39] Another unusual presentation was reported by Abdullah *et al*. They reported a young man's DLBCL metastasis to the heart; the tricuspid valve was also invaded in this case, in addition to the involvement of the right ventricle and atrium.[40]

DLBCL in the leukaemic phase

A 53-year-old man with a previous history of nasopharyngeal carcinoma three years before who completed chemoradiotherapy and was disease-free presented with a two-week history of B-symptoms, hyperleukocytosis (166.2×10^9/L) platelet count of 45×10^9/L and lactate dehydrogenase >8465 U/L. He was diagnosed with CD5+ ABC subtype of DLBCL. Immunohistochemical stain and gene studies showed Ki-67 (90%), negative c-myc, BCL2 and BCL6, and negative *c-MYC*. He received intravenous cyclophosphamide and oral prednisolone for cytoreduction, followed by 6 cycles of chemo-immunotherapy. However, he succumbed due to severe sepsis after the completion of therapy.[41]

DLBCL with haemophagocytic syndrome

Wan *et al*. also noted a 56-year-old woman investigated for pyrexia of unknown origin on bone marrow aspirate had histiocytic hyperplasia with increased hemophagocytic

activities. The bone marrow trephine biopsy showed atypical clusters of B-cells positive for CD20, low Ki-67 index and negative for CD10, BCL-2, BCL-6, and MUM-1. PET-CT scan noted an enlarged hypermetabolic spleen without lymphadenopathy. Splenic biopsy with immunohistochemical studies revealed ABC subtype of DLBCL. She was succumbed after two weeks from *Candida* and *Sternotrophomonas* septicemia.[41]

Recurrent tumours

A 67-year-old Chinese man in Perlis was diagnosed with recurrent lymphoma in non-healing leg ulcers six years after he had DLBCL diagnosed in a nasal cavity nodule. He had underlying varicose veins and stasis dermatitis associated with recurrent venous ulcers for 15 years. He was treated with eight cycles of R-CHOP and intrathecal methotrexate to achieve complete remission.[42]

A 25-year-old woman with features of superior vena cava obstruction was diagnosed with stage IIB non-Hodgkin's lymphoma. She achieved complete response with eight courses of CHOP with the disappearance of all the enlarged lymph nodes. She relapsed after 18 months, presenting with shortness of breath, loss of appetite, and loss of weight with a substantial mediastinal mass with right pleural effusion. She was treated with salvage therapy with ICE (ifosfamide, carboplatin, etoposide) followed by irradiation to the mediastinum. Imaging showed no residual mediastinal mass or mediastinal lymph nodes, but the bilateral ovarian tumours remained. Investigations revealed a markedly raised CA-125 (1216 U/ml), lactate dehydrogenase (3147 μmol/litre), and normal CEA and alpha-fetoprotein. Biopsy of both ovarian and omentum proved to be DLBCL, and the patient died postoperatively.[43]

A 45-year-old man with stage IV DLBCL presented 6 months after completing six cycles of R-CHOP chemotherapy with panuveitis. A month later, he developed a swollen optic disc and haemorrhagic retinitis and was treated as presumed CMV retinitis, and anti-tuberculous therapy was started after a positive Mantoux test. He then consented to a vitreous biopsy which showed atypical lymphoid cells suggestive of vitreoretinal lymphoma, and received intravitreal methotrexate.[44]

A 38-year-old man with GCB DLBCL of the cervical nodes who had completed 8 cycles of R-CHOP and 5 cycles of R-MATRix developed facial paralysis 20 months after chemotherapy, with preceding facial numbness and subsequent facial swelling, diplopia and pain. CT imaging revealed non-enhancing soft tissue density occupying the whole right middle ear cavity with bony erosion of the mastoid. He underwent surgery which improved his headache, pain and hearing and he received more chemotherapy. However, his disease progressed, and he succumbed.[45]

A 62-year-old Malay man who relapsed with DCBCL one year after therapy was found to have *S. stercoralis* in the pleural fluid and stools.[46]

The tumour microenvironment, nucleotide polymorphisms, tumour suppressor genes, oncogenes, and dysregulation of microRNA expression have been seen to reduce the drug's effectiveness and results in treatment resistance.[47,48] Younes, in 2013, reported higher expression of microRNA in tissue samples than in peripheral blood samples from DLBCL patients.[49]

MANAGEMENT

In treating DLBCL, the addition of rituximab to the standard chemotherapy regimens cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has shown a better prognosis.[50] However, 30% of patients had treatment resistance and relapsed within 24 months after diagnosis.[39] Ting *et al*. in their study, found that DLBCL patients with more than one extranodal site are 5.3 times more likely to be R-CHOP therapy-resistant or experience early disease relapse after R-CHOP therapy.[51]

In a retrospective study of 86 patients with DLBCL treated with R-CHOP-like and CHOP chemotherapy at a single centre. Gan *et al*., found that only 39 (45%) patients received rituximab in their treatment regime, and amongst patients receiving rithuximab only 12 (29%) patients had the recommended dose. The overall response (OR) and complete response (CR) rates were 88% and 81% respectively with R-CHOP-like and CHOP. There was no significant difference in OR and CR in patients who had rituximab and those without rituximab, which the authors highlighted may be a result of the inadequate dose of rituximab due to resource constraints. Those with an International Prognostic Index (IPI) score of ≤ 2 had a significant higher CR rate, progression-free survival (PFS), and overall survival ($p<0.001$).[52]

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

One target group of users for this review are clinicians assessing patients who present in similar ways. This collection of reports of the occurrence of BLBCL in various anatomical sites gives clinical a picture of what could be expected in Malaysia. It also guides any clinician interested in further research. It is a quick reference to work already done and cases already reported, so investigators know how to take knowledge a step further and not just repeat what has already been noted.

Genetic markers and proteins of gene expression that classify DLBCL into subgroups, such as GCB and non-GCB tumours, have prognostic significance and should be done in all cases. Authors of case reports should mention such findings as well as state treatment regimes used and survival outcomes so that future reference and analyses can make use of such findings. R-CHOP-like appears to be superior to CHOP-like treatment for DLBCL.

SECTION 3: FUTURE RESEARCH DIRECTION

One aim of research is that lymphoma treatment can be better targeted. Classifying DLBCL lymphoma with the immunohistochemical and genetic markers will hopefully lead to better knowledge of prognostic markers and knowing which therapeutic agent can be matched with these markers. Knowledge concerning what biochemical pathways these proteins and genes are involved in may lead to potential therapeutic targets. Research in Malaysia and this region needs to keep abreast with these frontiers.

Acknowledgements: We wish to thank Dr Cheong-Lieng Teng for his help with bibliographic search.

Authors' contribution: Kean Ghee LIM - conceived the idea, arranged for the literature search, assigned work and wrote sections of the paper and edited . Afshan SUMERA - wrote sections of the paper. Ismail Sattar BURUD - wrote section of the paper. Sunil Pazhayanur VENKATESWARAN – wrote section of the paper.

Conflict of interest: The authors declare no conflicts of interest.

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