Mantle Cell Lymphoma: An Epidemiological Review Of Hong Kong Patients

Introduction

Mantle cell lymphoma, previously known as diffuse small cleaved cell lymphoma and centrocytic lymphoma , is a low-grade non-Hodgkin lymphoma. It is a mature B cell neoplasm, consisting of mature B cells which have exited the bone marrow. Traditionally, MCL is known to be a very aggressive NHL despite its low-grade nature, and is considered to be incurable with current therapies. It typically afflicts the older population, with the median age of presentation of patients ranging from 60-68 . MCL has shown a clear male predisposition as well, with the male-to-female ratio of 3:1 . It is a rare lymphoma, which accounts for 8% of all NHL . Racially, it has a higher incidence in Caucasians than African Americans and Asians .

Pathogenesis

The initiating oncogenic mutation for MCL would be t(11,14)(q13;32), which concerns the oncogene bcl-1 on 11q13 and the immunoglobulin heavy chain gene on 14q32. Bcl-1 encodes for cyclin D1, a cell cycle protein regulating the progression of the cell from G1 phase to S phase . The translocation juxtaposes the bcl-1 gene next to the immunoglobulin heavy chain gene, which is highly active in mature B cells. This results in the overexpression of cyclin D1 in MCL cells, leading to disrupted cell cycle entry. It should be noted that t(11,14)(q13;32) itself alone does not have full oncogenic potential; oncogenicity is acquired through the gaining of additional genetic lesions and increased genomic instability. The WHO 2016 Classification has delineated 2 subtypes of MCL based on the clinical presentation and the cell of origin of the malignant clone, which in turn is differentiated by the expression status of the transcription factor Sex Determining Region Y-Box 11 (SOX11) . In classical MCL (cMCL), a more aggressive clinical course with general lymphadenopathy is common. De novo SOX11 expression is noted, which prevents virginal B cells from entering the germinal centre and participating in GC reactions. cMCL cells therefore have minimal IGHV mutation and are naïve-like as they have not experienced GC events. In contrast, the non-nodal subtype of MCL (nnMCL) has a more indolent course, and their presentation is leukaemic rather than with strong lymph node involvements. Splenomegaly is also common. SOX11 negativity allows the nnMCL cells to experience germinal centre reactions, with the resultant cells having a higher number of IGHV mutations resembling memory B cells. nnMCL cells also have a more stable karyotype and further progression into more malignant variants is less likely than cMCL . nnMCL accounts for about 10-20% of all MCL cases .

Morphology

Histologically, MCL consists of small to medium sized lymphoid cells with irregular nuclei . Chromatin is condensed with inconspicuous nucleoli, hence its low-grade classification. Large cells are uncommon . Cytologically, variants of MCL include classic, small cell, blastoid and pleomorphic. Cytological variations of MCL is associated with disease severity and survival, with blastoid and pleomorphic variants having a worse prognosis . Blastoid MCL has a higher

genomic instability with of additional mutations, such as tumour suppressor gene TP53 . It should be noted that blastoid transformation can occur from milder cytological variants through the gaining of additional genetic lesions, or from other haematological malignancies including chronic lymphocytic leukaemia (CLL), though the molecular events leading to such transformation is distinctive process known as MCL-variant Richter transformation. Lymph node involvements in MCL can be classified as distinctive patterns, namely mantle zone, nodular and diffuse by the extent of germinal centre disruption .

Immunocytochemistry

Upon staining, the neoplastic cells show positive staining for pan-B antigens, including CD19, CD20, CD22 with surface immunoglobulins IgM and IgD, in line with its B cell nature. Aberrant positivity of CD5, a T cell marker, is noted. Staining with cyclin D1 and cyclin D1/BCL1 is positive. Rare presentations of cyclin D1-negative MCL may yield negative cyclin D1, but positive stain on cyclin D2 or D3 . Negative stains include CD10 and 23, with the latter differentiating MCL from small lymphocytic lymphoma .

Patient presentation

Most patients present with late stage MCL, with 70% presenting with stage IV disease. Generalized, extensive lymphadenopathy and splenomegaly are common findings. A high proportion of patients also presents with extranodal involvements, with lymphoma cells spreading to mucosa-associated lymphatic tissues such as Waldeyer’s ring. GI involvement is also common, which mainly manifests in stomach and colon. Occasionally, incidental cases of lymphomatous polyposis are discovered when the patient undergoes colonoscopy . Bone marrow involvement is also extremely common. Leukaemic presentation can also be found in patients with nnMCL, or in late-stage patients with MCL cells spillover to peripheral blood. Pancytopenia may be observed if marrow failure occurs due to extensive bone marrow involvement. B symptoms, the triad of unintentional weight loss, night sweat and fever, may also be reported by the patient.

Treatment

Treatment for MCL remains diversified, but chemotherapy remains the mainstay of treatment. Considerations for regimens include patient age and risk stratification. The Mantle cell International Prognostic Index (MIPI), devised by the European MCL Network, is commonly used for the formulation of risk-adapted therapy. MIPI identifies patient age, Eastern Oncology Group (ECOG) Performance Status, LDH status and WBC count as independent prognostic factors that impact patient survival, and stratifies the patient pool into 3 categories: MIPI low-risk, MIPI median-risk and MIPI-high risk. The recent incorporation of proliferative index Ki67 takes into account of the proliferative activity of the neoplastic cells in vivo, and further improves the prognostic accuracy of MIPI as biological MIPI (bMIPI) . A higher proliferative index (>20%) is associated with a worse prognosis. For asymptomatic patients with an indolent disease presentation, or in the low-risk group, an observational approach should be adopted to avoid the initial use of aggressive therapy. Clinical interventions should be adopted when the patient progresses. For these patients, a commonly used regimen would be cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone. An anti-CD20 monoclonal antibody, most commonly rituximab, can also be added (RCHOP). RCHOP combination therapy yields a

satisfactory overall response rate as high as 96%, with a complete remission (CR) of 48% . For elderly patients, a milder approach should be considered in the view of cardiac toxicities of anthracycline-containing regimens and slower marrow recovery. Rituxumab-bendamustine (RB) is commonly used due to the less severe side effects of bendamustine, such as haematological toxicities and alopecia . Although less agents are used in the RB regimen when compared with RCHOP, it is shown that the efficacy of RB is similar to RCHOP, reaching an ORR of 89% . Other alkylating agents such as chlorambucil, and the purine analogue fludarabine are shown to be effective against MCL as well. For patients with a high tumour burden or patients in a palliative settting, hydroxyurea can be given for cytoreduction. For younger patients, an aggressive therapeutic approach should be considered to establish CR. R-HyperCVAD alternating with high dose cytarabine and methotrexate, or other similar modified regimens including Nordic Protocol, is considered the treatment of choice. However, severe haematological toxicity may lead to marrow suppression, and make marrow recovery difficult. It is shown that stem cell transplantation, including autologous and allogenic HSCT, improves survival outcomes . Younger patients that can tolerate total body irradiation and myeloablative conditioning should considered HSCT for consolidation.

Despite promising statistics is shown for different first line treatments of MCL, a high proportion of patients will stop responding to treatment and progress. A collection of studies has shown that the progression free survival (PFS) is 7-20 months, with the longest study reported 26 months. Relapse after attaining CR is extremely common as well.10-year OS for MCL is reported to be as low as 5-10% . Curative therapies for MCL remains lacking and more research is needed to develop novel agents. However, with respect to the latest researches concerning mantle cell lymphoma, both epidemiological and therapeutic research seems to be heavily biased towards Western Caucasian population. In particular, epidemiological information on Asian patients, especially Chinese, are lacking, with only 1 paper by Chim et al. providing details on the epidemiological features of Chinese MCL patients. Constructing an accurate epidemiological background on Chinese patients is paramount to provide a better picture for further clinical research. Therefore, the clinical and epidemiological data of MCL patients processed at Queen Mary Hospital (QMH)is organized and presented in this paper.

Patients

Due to administrative constraints between different hospital clusters, only patients with MCL who has been under the care of QMH at any point of their disease course were considered for the study. Biopsy records with a diagnosis of MCL established or confirmed by the Department of Pathology of Queen Mary Hospital during the period of 2003-2018 were recovered. A total of 83 biopsy records were reviewed. Among repeating records, the actual number of patients processed in the period is 65. Further selection of included patients was made, since some of these patients were non-Chinese or had limited information on the Clinical Management System (CMS). Exclusion criteria were non-Chinese ethnicity, concurrent diagnosis of any non-haematological malignancies, concurrent diagnosis of any non-therapy related haematological malignancies, and incomplete medical records. 41 patients were included in total.

Data collection

Medical records of the included patients were examined to extract relevant data for the study. Both CMS and Laboratory Information System (LIS) were accessed. Demographic data

including sex and age at diagnosis were collected. Clinical data such as dates of diagnosis, relapse and death (if applicable), hospital of diagnosis, case status and vital status were also reviewed. Patient presentation, including pattern of lymph node involvement, extranodal site(s) of involvement, bone marrow involvement, peripheral blood involvement, central nervous system (CNS) involvement, Ann Arbor stage and ECOG PS were also included. From the biopsy reports, the pathology of the neoplasm (blastoid/non-blastoid) were noted. SOX11 status and Ki67 percentage were noted, if mentioned in the original report. Serum LDH level at diagnosis was also included. Treatment protocols including induction regimens at diagnosis and relapse were collected as well. Participation at clinical trials was also assessed.

Calculations and statistics

Overall survival (OS) was chosen to present the survival statistics of the study. Due to the lack of clear documentation of the causes of death of some deceased patients, cancer-unrelated deaths could not be ruled out. To calculate survival, the date of diagnosis as stated on the biopsy report and the vital status on 15 October 2019 were used. Overall survival was estimated by Kaplan-Meier method, as provided on the software SPSS Statistics Version 23.

Results

Patient demographics

A total of 41 cases were presented to QMH during the period of 2003-2018. Less than half (48.8%) of the patients were diagnosed at QMH, with the majority being referred cases from other clusters and the private sector. Among the 41 patients, 85.4% were men. The male to female ratio was 5.8:1. The median age at diagnosis was 65 years, with the youngest patient at 46 and the oldest 84. The majority of the patients were elderly, with 53.7% greater than 65 years old.

Patient presentation, clinical and pathological characteristics

The majority of patients presented in late stage. 97% of patients were diagnosed with stage III(21.2%) and IV(75.8%) MCL. Majority of patients presented with lymphadenopathy, with 92.7% having lymph node involvement. Extranodal manifestation was common as 58.5% of patients had a least 1 extranodal organ involvement. Common organs involved were spleen (31.7%), GI tract (24.4%), liver (9.4%), bone (7.3%, n=3) and lung, parotid gland, pancreas and muscle (each 2.4%, n=1). A high incidence of bone marrow involvement (68.3%) was noted. Peripheral blood involvement was less common at 26.8%. Serum LDH was found to be elevated in 57.5% of patients. Blastoid presentation was noted in 4.9% of patients at diagnosis. A further 4.9% had undergone blastoid transformation during the course of their disease.

Treatment

All of the patients were treated by some form of chemotherapy at diagnosis. A total of 15 regimens were prescribed. First-line use of rituximab was noted in 75.6% of patients. 4.9% of patients received obinutuzumab as a part of induction therapy. Bendamustine was given to 24.4% of patients. 43.9% (n=18) of patients had participated in a clinical trial during their disease course. 22.2% (n=4) of patients participated in an ibrutinib trial while 83% (n=15)

participated in an arsenic trial. A 5.6% (n=1) participation was noted for a bortezomib trial and an anti-CD40 trial each. Repeated clinical trial participation was noted in 3 patients. 17.1% (n=7) of patients received a bone marrow transplant. 4 received autologous HSCT and the remaining 3 received allogenic HSCT. 7.3% (n=3) of patients were deemed transplant eligible but did not proceed to transplant. Reasons include death before transplant procedure and patient refusal.

Discussion

From our results, it is shown that there are a number of similarities between the epidemiological pattern of MCL in Western and Hong Kong Chinese patients. Elderly patients remained the majority in MCL, as the median age at diagnosis found in our study (65 years) fits the reported range of 65-70 years by Western studies , as well as the sole study on Hong Kong Chinese MCL patients by Chim et al. (65.5 years). A high proportion of elderly patients (53.7%) was also recorded in our study. However, it was significantly lower than that observed in a French study at 71.9% [m1]. More data from different regions is needed to confirm whether our patient constitution is indeed shifted to the younger side.

Male predominance is also confirmed in our study. Our study reported a male to female ratio of 5.8:1, which was significantly higher than that observed in previous Western studies ranging from 2-4 . It also exceeded the 3:1 ratio reported by Chim et al. The high number of males observed in our study may suggest a stronger male predominance in Chinese MCL patients, but the effect of extreme data cannot be ruled out.

Our study also confirmed that MCL patients typically presents in late stage. There was almost exclusive late stage presentation (97%) observed in our study, which was higher than the 80% reported by Chim et al. and the 75-80% in previous Western studies . Extranodal involvement is common, as exemplified by 58.5% patients having at least 1 extranodal site compromised at diagnosis. GI tract remains a common site of involvement, where 24.4% of patients presented with Gi involvement. This is consistent with that observed by Chim et al., who reported 20%. A high percentage of involvement at bone marrow (68.3%) and a considerable peripheral blood involvement (26.8%) were noted for our patients but the relevant statistics were not provided in both the French and Hong Kong studies.

Analysis of therapy regimens has proved to be difficult because of the large number of induction regimens attempted, and changes made to the regimens at mid-course further complicates the assessment of drug efficacy. Interestingly, due to the long timespan the study period covered, temporal changes of the induction regimen could be observed. The inclusion of rituximab in front-line therapy has increased as well. From limited application the late 1990s, rituximab has been incorporated to the standard induction regimen as seen in patients diagnosed in the 2010s. A high proportion of patients (43.9%) was included in a clinical trial, which was significantly higher than the French population’s 12% . This could be explained as QMH is a clinical trial centre. Only a limited percentage (17.1%) of patients received HSCT. A possible explanation could be extensive bone marrow involvement complicates the harvesting of haematopoietic stem cells for autologous transplantation. The high proportion of elderly patients also makes HSCT an unviable option due to age constraints.

Limitations

As our study was not a territory-wide study, only data processed by QMH could be retrieved. Therefore, calculating MCL incidence was not possible as data from other clusters could not be collected. Moreover, as only one centre is assessed, data collection is prone to bias and error. More data from other centres is needed to provide a complete picture of MCL epidemiology in Hong Kong and to confirm the features observed in our study. Given that QMH is the leading tertiary centre in the treatment and research of haematological diseases, confounders may affect the overall patient presentation. For example, patients referred from other secondary hospitals may have a more aggressive disease course to warrant sub-specialist care at QMH. The wide availability of clinical trials in QMH could also influence patient's therapy options, thus affecting the survival statistics observed.