Treating newly diagnosed Diffuse Large B-cell Lymphoma in the elderly patient with R-mini-CHOP: A single centre analytical retrospective observational study

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ABSTRACT

Introduction: Diffuse large B-cell lymphoma (DLBCL) forms the bulk of non-Hodgkin lymphoma (NHL) cases encountered in clinical practice among the elderly. For the majority of cases of DLBCL, treatment comprising of Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP) is suggested as first line chemotherapy. However, chemotherapy in the elderly population may be hampered by multiple factors, including reduced bone marrow reserves, significant comorbidities, and greater side effects from chemotherapy. Treatment as such aims to offer disease control and prolong life whilst minimising treatment related complications in this group of patients. Treatment with R-mini-CHOP, a reduced dose form of R-CHOP offers survival benefits and is recommended for treatment of elderly DLBCL patients and those who are frail. Our study examined local Malaysian experience of treating the newly diagnosed elderly DLBCL patient with R-mini-CHOP.

Materials and Methods: We retrieved retrospective data of all DLBCL patients aged >65 years old from the electronic medical records in Pusat Perubatan Universiti Malaya who received R-mini-CHOP. Treatment response was assessed by the overall response rate (ORR), defined as the proportion of patients attaining complete and partial remission after six cycles of treatment. We excluded patients with transformed lymphomas and relapsed refractory disease. For secondary analysis, we examined patients' treatment response according to their baseline demographic characteristics, development of complications during therapy as well as their survival in months from diagnosis.

Results: Our study identified 33 patients in the period of January 2017 till June 2023. The mean age of the sample cohort was 78 years old (Range from 66 to 86 years old). Majority of the samples had advanced stage lymphoma at initial diagnosis with n=21/33 (63.6%) having stage III and IV disease. At the end of treatment, one patient did not have assessment scans and hence was excluded from analysis. n=16/32 patients (50.0%) had attained ORR when analysed by intention to treat, n=14/32 (43.7%) attained complete response and n=2/32 (6.25%) attained partial response. When analysed for treatment response, those who attained ORR were more likely to have Stage 1 or 2 disease (p value = 0.028) and had statistically significant increased progression free survival (28.5 vs 5.5 months, p value <0.01) and overall survival (28.5 vs 9.0 months, p value = 0.03) compared to those who did not attain ORR. In terms of treatment associated complications, n=9/32 (28.1%) of patients developed severe infection necessitating hospitalization, n=14/32 (43.7%) developed at least Grade 2 and above cytopenias, and n=13/32 (41.6%) developed some other adverse side effects, most of which were mild to moderate in terms of severity.

Conclusion: The ORR for our patients treated with R-mini-CHOP was lower than other cohorts. We hypothesise that R-mini-CHOP alone may not offer adequate lymphoma control in our sample, especially for treatment of advanced stage DLBCL. Age alone is not an objective assessment of suitability for treatment; therefore, we suggest the use of geriatric prognostication tools to better ascertain patient groups who would benefit from full dose R-CHOP chemotherapy to improve response and survival.

KEYWORDS:
Lymphoma, Large B-cell, Diffuse, Aged, R-mini-CHOP

INTRODUCTION

Non-Hodgkin lymphoma (NHL) comprise a large group of lymphoproliferative disorders affecting a wide spectrum of patients. In the elderly population, diffuse large B-cell lymphoma (DLBCL) forms the bulk of NHL cases encountered in clinical practice. DLBCL is a high-grade lymphoma that commonly presents with a rapidly enlarging mass commonly of nodal origin, but there are cases of DLBCL arising from extranodal and extramedullary tissues in any part of the body.

Management of this heterogenous group of patients in the geriatric population poses a challenge for treating physicians and often requires shared decision making between physician and patient. For the majority of cases of DLBCL patients, chemotherapy with R-CHOP has long been suggested as first line chemotherapy.[1] However, chemotherapy in the elderly population may be hampered by multiple factors, including reduced bone marrow reserves, significant comorbidities (e.g. Heart failure precluding use of anthralcycline-based chemotherapy, renal and hepatic impairment possibly requiring dose adjustment of chemotherapy drugs), and higher morbidity from side effects

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of chemotherapy (e.g. Chemotherapy using vinca-alkaloid based treatments resulting in peripheral neuropathy).[2] Treating the frail and elderly DLBCL patient with a reduced dose of chemotherapy seeks to offer adequate disease control and prolong survival whilst minimising treatment related toxicities.

Treatment with R-mini-CHOP involves administering chemotherapy at a pre-specified lower dose (Approximately 50% reduction in the dose of Cyclophosphamide, Doxorubicin, and Vincristine). In its pivotal single arm prospective trial in 2010, R-mini-CHOP showed survival benefit in patients above 80 years old, and offered a good compromise between treatment efficacy and safety. After a median follow up of 20 months (Range 0-45) in N=149 patients, the trial reported a median overall survival of 29 months and progression free survival of 21 months. Fifty eight deaths occurred in the cohort (n=58/149, 38.9%) for which n=33/58 (56.8%) were attributable to disease progression and n=12/58 (20.7%) due to treatment related complications. Overall response rate (ORR) was achieved in n=109/149 (73%) of patients. In terms of treatment toxicity, n=59/149 (39.5%) developed severe neutropenia and n=11/149 (7.3%) developed febrile neutropenia, n=56/149 (37.5%) developed thrombocytopenia and n=133/149 (89.2%) had anaemia, most of which were Grade 1-2 in terms of severity.[3] Since then, R-mini-CHOP has been adopted as a treatment modality in guidelines for patients above 80 years old or in those younger than 80 years old but with other significant comorbidities or impaired performance status.[4-6]

Our study is a retrospective observational study looking at the characteristics and outcomes of treating elderly DLBCL patients with R-mini-CHOP in a local Malaysian population.

MATERIALS AND METHODS

We identified all DLBCL patients who had received R-mini-CHOP through a retrospective review of chemotherapy charts and daycare visits data. Patients younger than 65 years of age, those who had relapsed-refractory DLBCL or those with transformed lymphoma were excluded. The choice of patients aged 65 years old and above receiving R-mini-CHOP as opposed to 80 years old as per international guidelines was at the discretion of the treating haematologists, seeking to minimise treatment related toxicities. This arbitrary institutional practice takes into consideration that the Malaysian authorities use a cutoff point of 60 years chronological age to define the 'older persons'.[7]

Patient information was then retrieved from the electronic medical records at Pusat Perubatan Universiti Malaya. The diagnosis of DLBCL was confirmed through histological and appropriate immunophenotyping testing. Data was collected for each patient by manual review of patient records – Age, sex, comorbidities at diagnosis, baseline Eastern Cooperative Oncology Group (ECOG) performance score, baseline lactate dehydrogenase (LDH) level, lymphoma staging at diagnosis, extranodal disease involvement at diagnosis, date of treatment, treatment received, number of treatment cycles received, treatment response at interim and end of treatment, development of cytopenias and sepsis, adverse outcomes from treatment, months of survival from start of treatment, and death as of 31/12/2023. Data on survival was censored after 31/12/2023.

Response was assessed by the ORR according to the Lugano classification, defined as the proportion of patients attaining complete and partial remission after six cycles of treatment.[8] Assessment of response was by demonstration of reduction in size and uptake of fluorodeoxyglucose F18 (FDG) by diseased tissue on imaging with either fluorodeoxyglucose-18 positron emission tomography (FDG-PETCT) or computed tomography (CT) scan. During the course of treatment, should a patient develop complications from therapy, the adverse event was recorded and severity assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5 criteria.[9] The CTCAE grading is a five-level scale from 1 to 5: Grade 1 mild, Grade 2 moderate, Grade 3 severe, Grade 4 life threatening, and Grade 5 death related to adverse events.

Data analysis was performed with SPSS software version 27. Patient demographics was expressed with descriptive statistics. At end of treatment, patients who attained ORR (Responders) were compared with those who did not attain ORR (Non-responders) for differences in terms of baseline demographics and treatment related complications. Differences between responders and non-responders were assessed by Chi-square test/ Fishers exact test for categorical data and respective parametric/non parametric test for scale data. Where appropriate, an odds ratio was calculated at significance level $\alpha = 0.05$. Survival data was expressed as median number of months of survival. Progression free survival is defined as the duration of survival till disease relapse/ progression or death of patient. Overall survival is the duration of survival till death from any cause.

RESULTS

A total of 36 patients were identified from January 2017 till June 2023. Two patients were excluded as they had transformed lymphoma. Of the 34 patients identified who received treatment with R-mini-CHOP, one had refractory disease and hence was excluded from analysis (Figure 1).

The mean age of our sample cohort was 78 years old (Range 66 to 88 years old). n=13/33 (39.3%) of the patients were female. Majority of patients had some comorbid medical condition at diagnosis of DLBCL with hypertension in n=18/33 patients (54.5%), diabetes mellitus in n=12/33 patients (36.3%), heart disease in n=9/33 patients (27.2%) and chronic kidney disease in n=3/33 patients (9.1%). Notably, n=19/33 (57.6%) of patients had two and more underlying comorbidities at initial diagnosis of DLBCL. At initial diagnosis, n=21/33 of patients (63.6%) had stage 3 and 4 disease and extranodal disease was present in n=25/33 patients (75.7%).

n=22/33 of patients (66.7%) receiving R-mini-CHOP completed at least six cycles of treatment (Figure 2(i)). One patient was lost to follow up before assessment imaging and was excluded from our final analysis. Of the remaining patients who did not complete treatment, n=5/10 (50.0%)

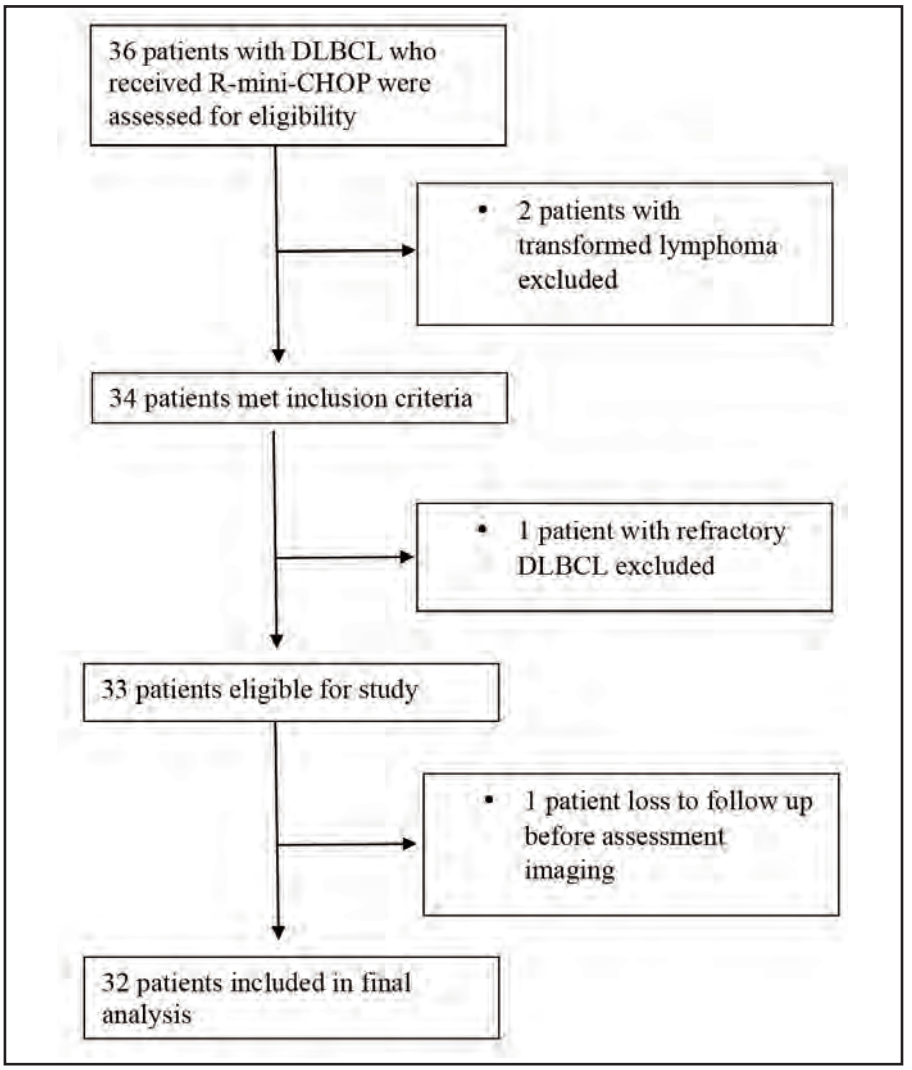

Fig. 1: Screening and classification of patients

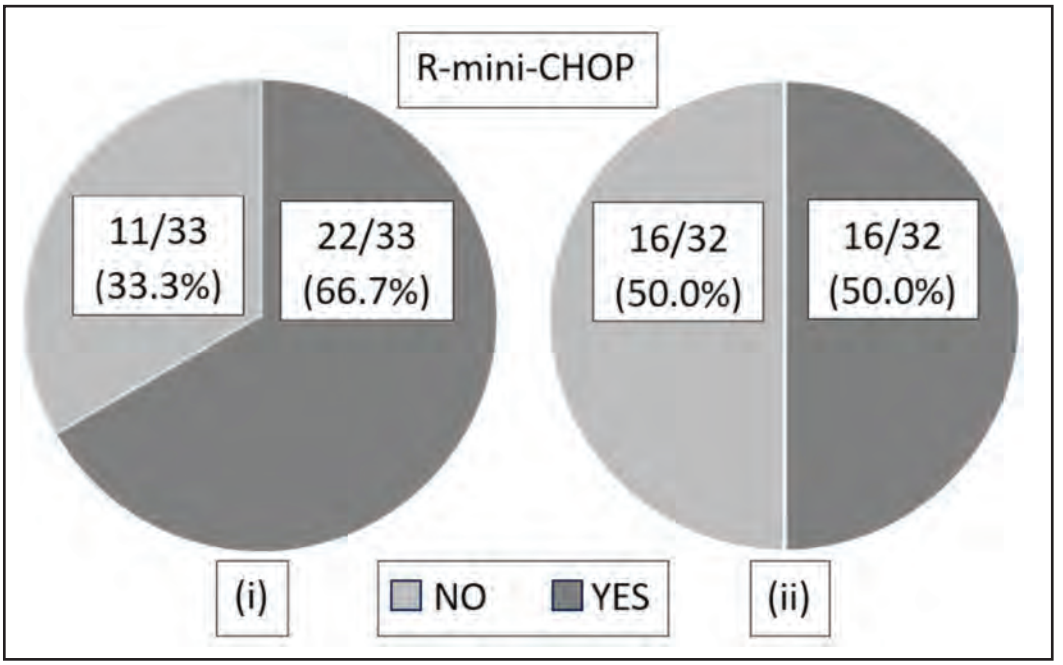

Fig. 2: (i) Proportion of patients receiving R-mini-CHOP completing at least 6 cycles of treatment. (ii) Proportion of patients receiving R-mini-CHOP attaining ORR

Table I: Comparison between treatment non-responder and responders for R-mini-CHOP in terms of baseline demographic characteristics

	Non Responder (n= 16)	Responder (n=16)	Odds Ratio [95% confidence interval]	p-value[a]
Mean age[b] – year (Standard deviation)	76.7 (4.95)	78.5 (4.02)	-	0.264
Gender – female n (%)	7 (43.8)	6 (37.5)	0.77 [0.19-3.17]	0.719
Comorbidities at diagnosis				
Diabetes mellitus – n (%)	5 (31.3)	6 (37.5)	1.32 [0.31-5.70]	0.710
Hypertension – n (%)	9 (56.3)	8 (50.0)	0.78 [0.19-3.13]	0.723
Cardiovascular disease[c]- n (%)	3 (18.8)	5 (31.3)	1.97 [0.38-10.17]	0.685
Chronic kidney disease[d]- n (%)	2 (12.5)	1 (6.3)	0.47 [0.04-5.73]	>0.995
ECOG performance status[e]				
≤ 2 – n (%)	15 (93.8)	16 (100)	-	>0.995
3-4 – n (%)	1 (6.3)	0 (0)		
Median Lactate dehydrogenase (LDH) at diagnosis – IU/L (Interquartile range, IQR)	293 (350)	209 (142)	-	0.105[f]
Extranodal involvement at diagnosis – n (%)	14 (87.5)	10 (62.5)	0.24 [0.04- 1.43]	0.22
Stage of disease at diagnosis				
1-2 – n (%)	3 (18.8)	9 (56.3)	5.57 [1.13-27.52]	0.028
3-4 – n (%)	13 (81.3)	7 (43.8)	0.18 [0.04-0.89]	

[a] Unless specified, difference between non – responders and responders were tested using Chi square test or Fisher exact test at statistical significance p< 0.05
[b] Independent samples T test was used to compare means in sample
[c] Cardiovascular disease was defined as having previously diagnosed with ischemic heart disease, heart failure, valvular heart disease, arrhythmia
[d] Chronic kidney disease was defined as having previous glomerular filtration rate <60 ml/min/1.73m2 for more than 3 months
[e] Eastern Cooperative Oncology Group performance status at diagnosis
[f] Independent samples Mann-Whitney U test used to compare medians in sample

Table II: Comparison between treatment non-responder and responders for R-mini-CHOP in terms of treatment related complications and survival in months

	Non Responder (n= 16)	Responder (n=16)	Odds Ratio [95% confidence interval]	p-value
Developed cytopenia during treatment[a] - n (%)	8 (50.0)	6 (37.5)	0.60 [0.15-2.46]	0.476
Developed sepsis or hospitalised for infection during treatment – n (%)	6 (37.5)	3 (18.8)	0.39 [0.08-1.93]	0.433
Developed other severe adverse effects during treatment[b] – n(%)	3 (18.8)	1 (6.3)	0.29 [0.03-3.13]	0.600
Death[c] – n (%)	10 (62.5)	1 (6.3)	0.04 [0.01-0.39]	<0.01
Progression free survival – median months (IQR)	5.5 (4)	28.5 (23)	-	<0.01[d]
Overall survival – median months (IQR)	9.0 (28)	28.5 (22)	-	0.03[d]

[a] Cytopenias defined as haemoglobin ≤ 10g/dL, absolute neutrophil count < 1 x 10^9/L, platelet < 150 x 10^9/L or more than one of the above defined cytopenias during the course of treatment
[b] Severe adverse effects was defined as ≥ Grade 3 according to CTCAE Version 5
[c] Death as of 31/12/2023
[d] Independent samples Mann-Whitney U test used to compare medians in sample

were due to disease progression, n=2/10 (20.0%) due to drug intolerance, and the remaining n=3/10 (30.0%) had completed treatment as determined by the treating physician. At end of treatment, n=16/32 patients (50.0%) had attained ORR by intention to treat analysis; n=14/32 (43.7%) attained complete response and n=2/32 (6.25%) attained partial response (Figure 2(ii)). When analysis was limited only to the 22 patients who completed six cycles of treatment; limiting effects from suboptimal drug administration either due to intolerance or change in chemotherapy regime, n=12/22 (54.5%) had attained complete remission, n=2/22 (9.1%) had partial remission, giving an adjusted ORR of 63.6%.

Table I demonstrates comparison between non-responders and responders in terms of baseline demographic characteristics. Among the various variables, stage of disease at diagnosis was found to correlate with treatment response whereby responders had a higher proportion of patients with Stage 1 and 2 disease (p-value = 0.028). There was no significant difference between non-responders versus responders in terms of mean age, gender, comorbidities at diagnosis, baseline LDH, extranodal involvement, or baseline ECOG performance status.

Table II illustrates safety outcomes comparing treatment related complications between non-responders and responders as well as associated survival outcomes. n=14/32 (43.7%) developed at least Grade 2 and above cytopenias, n=9/32 (28.1%) of patients developed severe infection necessitating hospitalization, and n=13/32 (41.6%) developed some other adverse side effects while undergoing treatment, from which n=4 were Grade 3 and above in terms of CTCAE classification. Most of these adverse effects were

mild to moderate (Grade 1-2) diarrhoea, vomiting, paraesthesia, and alopecia; however there was 1 episode of Grade 4 upper gastrointestinal bleeding, 1 episode of Grade 3 vomiting and 2 Grade 3 thromboembolic events. There was no statistically significant difference between responders and non-responders in terms of development of cytopenias [n=6 (37.5%) vs n=8 (50.0%), p-value = 0.476], development of sepsis [n=3 (18.8%) vs n=6 (37.5%), p-value = 0.433] and development of other Grade 3 above complications [n=1 (6.3%) vs n=3 (18.8%), p-value = 0.600].

In terms of survival, the median progression free survival in months for the entire cohort was 13 (IQR 27) and median overall survival was 26 (IQR 26). Responders had statistically significant increased progression free survival (28.5 vs 5.5 months, p-value <0.01) and overall survival (28.5 vs 9.0 months, p-value = 0.03) compared to non-responders (Table II).

DISCUSSION

In our sample cohort, majority of patients completed six cycles of treatment, n= 22/33 (66.7%) but only n= 16/32 (50.0%) attained ORR. In a retrospective review of the Dutch cancer registry, Al-Sarayfi et al (10) examined response of patients receiving R-mini-CHOP (Median number of cycles six, range one to eight) against a propensity matched cohort receiving full dose R-CHOP. Our sample ORR for R-mini-CHOP is lower than the ORR of 72% in the aforementioned study.[10] We are unable to ascertain causality for the lower ORR recorded in our cohort. However, as the reason for patients not completing treatment in our cohort was mainly related to disease progression, n=5/10 (50.0%), we hypothesise that R-mini-CHOP may not offer adequate lymphoma control in our sample, especially for treatment of advanced stage DLBCL.

The study by Al-Sarayfi et al (10) attempted to determine if the better tolerability of R-mini-CHOP would be offset by possible reduced disease response. While there was reported poorer ORR, progression free survival and overall survival in the R-mini-CHOP cohort as compared to the R-CHOP cohort, the study did not report the occurrence of treatment related complications or toxicities in the sample, which may hypothetically be higher in the R-CHOP cohort.[10]

When compared with the earlier Phase 2 trial by Peyrade et al (3), our cohort had lower progression free survival (13 vs 21 months) but comparable overall survival (26 vs 29 months).[3] Death occurred in n=11/32 (34.3%) of our patient cohort similar to the aforementioned study (38.6%).

In our cohort, patients who responded to R-mini-CHOP had improved progression free survival (28.5 vs 5.5 months) and overall survival (28.5 vs 9.0 months) compared to non-responders. In terms of treatment toxicity, n=14/32 (43.7%) of our patients developed at least Grade 2 and above cytopenias and n=9/32 (28.1%) developed sepsis requiring hospitalisation. This finding supports earlier and more aggressive supportive interventions with blood products transfusion and the use of prophylactic granulocyte colony stimulating factors during treatment. For those at high risk of developing infective complications, a consideration should be given for antimicrobial prophylaxis therapy.[11]

We have identified several limitations in our study. Firstly, our small sample size of N=33 patients may be underpowered to detect true effect sizes. Furthermore, assessment of patient's performance status or frailty was done subjectively by the treating haematologist using only the patient's ECOG score. Patients who are more frail at diagnosis may have been selected for treatment with R-mini-CHOP, hence negatively impacting the treatment outcomes.

Due to the retrospective nature of our study design, there is a chance of biases introduced in our study. Misclassification bias can happen during data collection where variables can be inappropriately coded. Selection bias can be introduced as patients were sampled only from a single medical centre in an urban setting, and results may not be generalisable to other patient populations. Study outcomes may be affected by other unsampled variables leading to confounding, and a causal link between treatment and outcomes cannot be determined.[12]

There is a lack of information of the DLBCL cell of origin or genetic profiling, which increasingly is shown to affect disease outcomes.[13] It is unclear if the lower than expected ORR for our patient cohort might possibly be due to higher prevalence of adverse genetic and molecular profiles in our population.

The use of R-mini-CHOP in a younger patient cohort than that reported in literature and guidelines (65 years old vs 80 years old) may offer explanation for the lower ORR seen in our study, as the attenuated treatment may not offer adequate disease control compared to full dose chemotherapy. Lastly, due to the widespread disruption of health services during the COVID-19 pandemic, it is unclear from our study how the pandemic had impacted treatment decisions, follow up or outcomes.

Moving forward, further dedicated geriatric oncology studies are warranted to improve outcomes for this diverse group of patients, whom unfortunately are underrepresented in many clinical trials.[14-15] To improve assessment of elderly patients for selection of treatments, use of screening tools like G8, Elderly Prognostic Index or Clinical Frailty Score should be encouraged, with frail patients identified then referred to a geriatrician for comprehensive assessment.[14-15] Proper patient selection for treatment is important as fit elderly patients benefit similarly from curative treatment regimes such as full dose R-CHOP chemotherapy as compared to younger patients.[16] A follow up prospective cohort study of all elderly DLBCL patients treated with the various chemotherapy regimes including R-CHOP and R-mini-CHOP could better identify patient profiles best suited for each treatment arm.

CONCLUSION

Whilst preliminary, our findings suggest that R-mini-CHOP may not adequately control DLBCL, especially in patients who present with advanced stage disease. As such, due consideration should be given in selecting suitable patients

who may otherwise benefit from full dose R-CHOP chemotherapy in the newly diagnosed elderly patient with DLBCL.

Our study highlights part of the complexities of managing malignancy in a diverse and possibly frail patient population, emphasising that there is no 'one size fits all' treatment. We concur with reported literature highlighting the role of geriatric assessments in a multi-disciplinary team to better individualise treatment. We also report Malaysian data, which could serve as a benchmark against other reported patient outcomes elsewhere.

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