Chung Shan Medical Journal 2020; 31:67-72

Original Article

# Treatment outcomes of diffuse large B cell lymphoma in elderly patients based on a seven-year experience in Chung Shan Medical University Hospital

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**Background:** To assess the clinical outcomes of elderly patients aged > 65 years diagnosed with diffuse large B cell lymphoma (DLBCL).

**Materials and Methods:** This is a single-institute, retrospective, cohort study. A total of 44 elderly DLBCL patients were enrolled from Jan 2011 to Dec 2017. Clinical characteristics were retrospectively reviewed based on medical records. Cox proportional hazards model was applied to univariate and multivariate analyses. Survival was estimated using Kaplan-Meier method and log-rank test.

**Results:** A total of 44 elderly DLBCL patients were enrolled in our study. Most presented with poor performance status (ECOG > 1, 68.6%, 24/35) and advanced stage (Ann Arbor staging > II, 65.1%, 28/43). Median follow-up time and overall survival (OS) were 11.2 and 13.8 months, respectively. Patients with standard-dose treatment showed better OS than those with reduced-dose treatment (median OS, 28.0 vs. 14.2 months, $P = 0.135$). On univariate analysis, performance status ($P = 0.023$), Ann Arbor staging ($P = 0.018$), extranodal involvement ($P = 0.019$), and elevated LDH ($P = 0.008$) were significant factors for OS. However, only elevated LDH was an independent factor (hazard ratio [HR], 95% confidence index [CI], 3.239 (1.152-9.110), $P = 0.026$). Performance status (ECOG > 1, HR [95% CI], 4.711[0.991-22.396], P = 0.051) was an independent factor on multivariate analysis.

**Conclusion:** Standard-dose chemoregimens are suggested for elderly DLBCL patients. Elevated LDH and performance status are independent factors in clinical practice.

**Keywords:** elderly, diffuse large B cell lymphoma, LDH, ECOG

## Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma (NHL) and the R-CHOP regimen (rituximab plus cyclophosphamide, vincristine, doxorubicin, and prednisolone) is the standard treatment protocol for these patients.[1] In Taiwan, rituximab, an anti-CD20 monoclonal antibody, was

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approved by the Bureau of National Health Insurance of Taiwan as first-line therapy in December 2003. Many studies on DLBCL have shown that the efficacy of the R-CHOP regimen in Taiwan is equal to that achieved globally.[2,3]

As human lifespans increase, the number of elderly cancer patients is expected to rise.[4] Whether the same treatment strategy should be used in elderly patients and younger patients has been a subject of interest in different cancer types.[5-7] In Taiwan, studies on the outcomes of DLBCL in elderly patients have been rare. Appropriate chemoregimens, dosage, and scheduling are difficult to determine in elderly patients, especially in terms of the need to balance efficacy and toxicity.

In this study, we retrospectively enrolled elderly DLBCL patients diagnosed at Chung Shan Medical University Hospital. Clinical outcomes and treatment strategies were analyzed. The results of this study provide information about the outcomes of elderly DLBCL patients in Taiwan, which can lead to improvements in treatment methods for this population.

## Patients and Methods

*Study population and data collection*

Elderly DLBCL patients, aged 65 and over, were retrospectively enrolled in this study between January 1, 2011, and December 31, 2017. All enrolled patients were pathologically diagnosed with DLBCL and treated according to the multidisciplinary guidelines of Chung Shan Medical University. Patients without pathologic diagnosis or who had secondary malignancies were excluded.

The baseline characteristics of patients were collected at the time of diagnosis. These included patient demographics, complete blood count, serum biochemistry parameters, performance status (PS), Ann Arbor stage, and treatment methods. Medical records were obtained from the Chung Shan Medical University Hospital Cancer Center Cancer Registry.

*Comorbidity index and prognostic factors*

Comorbidities refer to coexisting chronic illnesses and have been well documented with increasing trends associated with age in elderly patients.[8] The number of comorbidities was recorded according to the National Institute on Aging and the National Cancer Institute SEER collaborative study, which was developed to describe the severity of comorbidity burden based on medical records. Comorbidities include arthritis, chronic obstructive pulmonary disease, diabetes, gastrointestinal problems, heart conditions, and hypertension.[8,9] The numbers of comorbidities in each patient were totaled in our study.

*Treatment*

The first-line therapy for all patients was chemotherapy combined with rituximab. In elderly patients, combination chemoregimens depend on physician evaluation. The CHOP dosing schedule has been described previously.[10] For patients with borderline cardiac function and poor PS, the dosage of doxorubicin is modified or replaced with epirubicin, producing CHOP-like regimens or mini-CHOP/CEOP.[11]

*Statistical analysis*

The correlations among clinicopathological variables were analyzed using $\chi^2$ test or Fisher's exact test. Cox proportional hazards model was applied to univariate and multivariate analyses. Attending physicians assessed the response based on Cheson's criteria.[12] Overall survival (OS) was calculated from the date of disease diagnosis to the date of death or the date of last evaluation. The final follow-up date was December 31, 2018. Survival was estimated using Kaplan-Meier method and log-rank test was used to compare survival curves. Variables with $P$ values $< 0.05$ on univariate analyses were entered into multivariate analysis models. A two-sided $P$ value of $< 0.05$ was regarded as statistically significant. SPSS statistical software (version 19.0, SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

## Results

*Patient characteristics*

A total of 44 elderly DLBCL patients were enrolled between Jan 2011 and Dec 2017. Most presented with poor PS (ECOG > 1, 68.6%, 24/35)

**Table 1. Basic characteristics of elderly DLBCL patients**

| | N = 44 |
|---|---|
| Age > 75 | 25(56.8) |
| Available | 44 |
| Male | 20(45.5) |
| Available | 44 |
| ECOG > 1 | 24(68.6) |
| Available | 35 |
| Ann Arbor staging > II | 28(65.1) |
| Available | 43 |
| Bone marrow involvement | 8(44.4) |
| Available | 18 |
| Extranodal involvement | 20(45.5) |
| Available | 44 |
| Comorbidity score >1 | 18(42.9) |
| Available | 42 |
| Pre-treatment biochemistry | |
| Albumin < 3.5 | 14(34.1) |
| Available | 41 |
| LDH > UNL | 23(54.8) |
| Available | 42 |
| Chemotherapy | |
| Yes | 35(81.4) |
| Standard dose | 12 |
| Reduced dose | 23 |
| No | 8(18.6) |
| Available | 43 |

and advanced stage (Ann Arbor staging > II, 65.1%, 28/43). Nearly 20% did not undergo chemotherapy (18.6%, 8/43). Among the remaining patients, most received reduced-dose chemoregimens (65.7%, 23/35). The basic characteristics of these patients are shown in Table 1.

*Survival outcome*

The median OS was 13.8 months and the median follow-up time was 11.2 months. In our study, 81.4% (35/43) of patients received systemic chemotherapy. However, 65.7% (23/35) of patients who received chemotherapy did so at a reduced dose. Patients treated with standard dose showed better OS than those treated with reduced dose. However, the difference was not statistically significant (median OS, 28.0 vs. 14.2 months, $P = 0.135$).

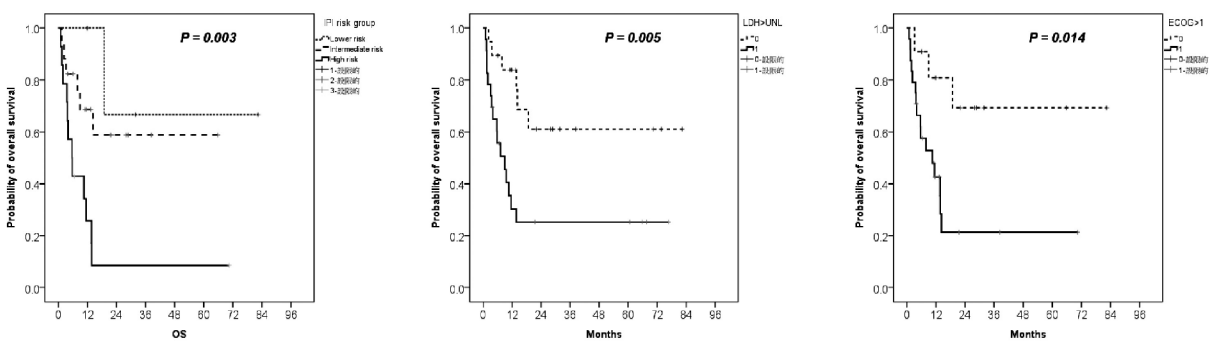
*Cox regression analyses for overall survival*

**Table 2. Univariate and multivariate Cox regression analyses for overall survival**

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | *P* value | HR(95% CI) | *P* value | HR(95% CI) |
| Age > 75 | 0.271 | 1.594(0.695-3.654) | | |
| Male | 0.267 | 0.625(0.272-1.433) | | |
| ECOG > 1 | 0.023 | 4.287(1.222-15.042) | 0.051 | 4.711(0.991-22.396) |
| Ann Arbor staging > II | 0.018 | 3.724(1.254-11.054) | 0.129 | 3.364(0.701-16.132) |
| Bone marrow involvement | 0.193 | 2.635(0.613-11.324) | | |
| Extranodal involvement | 0.019 | 2.717(1.180-6.259) | 0.508 | 0.622(0.153-2.536) |
| Comorbidity score >1 | 0.793 | 1.119(0.482-2.596) | | |
| Pre-treatment biochemistry | | | | |
| Albumin < 3.5 | 0.139 | 1.864(0.816-4.260) | | |
| LDH > UNL | 0.008 | 3.583(1.390-9.236) | 0.026 | 3.239(1.152-9.110) |
| Chemotherapy | | | | |
| Yes vs. No | 0.684 | 0.813(0.301-2.198) | | |
| Standard vs. reduced dose | 0.145 | 2.164(0.766-6.117) | | |

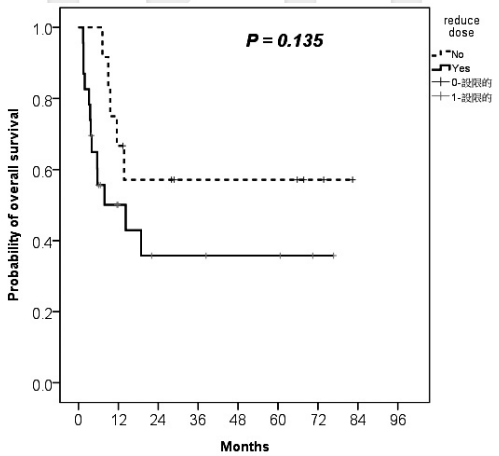
Univariate and multivariate Cox regression analyses for OS were performed. On univariate analysis, PS ($P$ = 0.023), Ann Arbor staging ($P$ = 0.018), extranodal involvement ($P$ = 0.019), and elevated LDH ($P$ = 0.008) were significant. On multivariate Cox regression, only elevated LDH was independent (hazard ratio [HR], 95% confidence index [CI], 3.239 (1.152-9.110), $P$ = 0.026). In addition, although PS was not significant on multivariate analysis, it was considered important due to the small sample size (ECOG > 1, HR [95% CI], 4.711[0.991-22.396], P = 0.051) (Table 2). As shown in Figure 1, among patients classified according to international prognostic index (IPI) scoring system, outcomes were significantly different with 5-year OS rates for low- , intermediate- , and high-risk patients of 66.7%, 58.8%, and 8.6%, respectively (P = 0.003). In addition, patients with elevated LDH or poor PS showed poor outcomes (5-year OS, LDH > UNL vs. LDH < UNL, 25.3% vs.

**Figure 1. Independent prognostic factors of OS in elderly DLBCL patients**




Among our 44 elderly DLBCL patients, (a) performance status ($P$ = 0.014), (b) elevated LDH ($P$ = 0.005), and (c) international prognostic index score ($P$ = 0.003) were important factors for overall survival.

**Figure 2. Overall survival of patients with standard- or reduced- dose chemotherapy.**




A total of 35 patients (81.4%, 35/43) were fit for chemotherapy. Standard-dose therapy (34.3%, 12/35) was associated with better OS than reduced-dose therapy (65.7%, 23/35) (P = 0.135).

61.0%, *P* = 0.005; ECOG > 1 vs. ECOG < 1, 21.3% vs. 69.3%, P = 0.014) (Figure 1).

## Discussion

This retrospective study was conducted to analyze the outcomes of elderly DLBCL patients in central Taiwan. According to IPI scores, 5-year overall survival rates of low-, intermediate-, and high- risk patients were 66.7%, 58.8%, and 8.6%, respectively (*P* = 0.003). Standard-dose chemoregimens are suggested but require advanced evaluation. Elevated LDH and poor PS are independent poor prognostic factors. The results of this study provide valuable information for clinical practice.

Many studies have shown that PS is an independent factor in terms of OS following cancer treatments, especially among elderly patients, as PS is closely related to comorbidities.[13,14] In a study by Huang et al., PS was found to reflect the interactions among age, comorbidities, and tumor burden.[15] In the present study, PS and elevated LDH were significantly associated with OS. However, PS was not an independent prognostic factor for OS. This might be due to the small study population. Overall, these were important factors for determining the treatment outcomes of elderly DLBCL patients.

Another issue is whether elderly DLBCL patients should be treated as intensively as younger DLBCL patients. In a study by Cho et al., median progression-free survival (PFS) and OS of > 65-year-old DLBCL patients were 15 and 21 months, respectively.[16] Besides, very old age (> 81 years) and bone marrow involvement are associated with poorer PFS and OS.[16] Anthracycline-based chemoregimen, which has been demonstrated to produce cardiac toxicity, is suggested for elderly patients due to the lack of randomized control studies of transitional and other novel agents, such as ibrutinib, brentuximab vedotin, and lenalidomide.[17] In Taiwan, Cheng et al. have suggested that reduced-dose R-CHOP (RD-R-CHOP) is more effective than rituximab plus bendamustine (BR) for treating elderly DLBCL patients. In their study, the overall response rate and OS of RD-R-CHOP and BR were 79.4% versus 50% (P = 0.027) and 39.0 versus 11.2 months (P = 0.035), respectively.[18] From the above, anthracycline-based therapy is still indicated for elderly patients who are medically fit for chemotherapy. In the present study, although 18.6% (8/43) of patients did not receive chemotherapy, among those deemed fit for treatment, standard-dose therapy was suggested if PS was good.

There were some limitations to our study. First, it included only a small study population. A larger cohort is needed to validate our findings. Due to the age of the patients, chemoregimens were modified according to physician evaluation. Although based on the multidisciplinary guidelines of the lymphoma group of Chung Shan Medical University Hospital, there were no uniform chemoregimens for comparing the outcomes after treatment. Third, as this was a retrospective study, there may have been coding errors in the medical records.

In conclusion, there are increasing numbers of elderly DLBCL patients. A total of 44 elderly DLBCL patients were retrospectively analyzed with median follow-up time and OS of 11.2 and 13.8 months, respectively. Elevated LDH and PS are important factors associated with OS. For patients who are medically fit, standard-dose treatment results in better OS than reduced-dose treatment. Comprehensive geriatric assessment is needed to evaluate PS. Moreover, large prospective studies on

the treatment outcomes of elderly DLBCL patients are warranted in the future.

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