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Original Article

Analysis of Clinical Factors and Mortality in Diffuse Large B-cell Lymphoma Patients Over or Under 80 Years of Age

Shinji Hasebe [a], Keiko Tanaka [b, c], Yoshihiro Miyake [b, c], Hiroaki Asai [d], Kazuto Takeuchi [d], Tomomi Fujii [a], Hitoshi Kawazoe [e], Kazushi Tanimoto [d], Jun Yamanouchi [d], Taichi Azuma [d], Masaki Yasukawa [d], Yoshihiro Yakushijin [a *]

[a] Department of Clinical Oncology, Ehime University Graduate School of Medicine, Ehime, Japan, [b] Department of Epidemiology and Preventive Medicine, Ehime University Graduate School of Medicine, Ehime, Japan, [c] Epidemiology and Medical Statistics Unit, Translational Research Center, Ehime University Hospital, Ehime, Japan, [d] Department of Hematology, Clinical Immunology and Infectious Disease, Ehime University Graduate School of Medicine, Ehime, Japan, [e] Division of Pharmacy, Ehime University Hospital, Ehime, Japan

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SUMMARY

Background: The prognosis of diffuse large B-cell lymphoma (DLBCL) is remarkably improved after R-CHOP therapy. However, there are few detailed reports regarding very elderly DLBCL patients. We investigated relationships between prognostic factors and mortality risk in DLBCL patients, especially those aged 80 years or more.

Methods: The study subjects consisted of 141 patients newly-diagnosed with *de novo* DLBCL. Information regarding age, sex, stage, performance status (PS), lactate dehydrogenase (LDH), extranodal (EN) involvement, and therapies was available.

Results: For the 141 patients, the female sex was significantly inversely related to mortality, whereas age ≥80 years, PS ≥2, and non-standard therapy were significantly positively associated with death. No associations were observed between death and stage, LDH, or EN. When classifying patients by age (<80 [n = 108] and ≥80 [n = 33] years), a significant inverse association between female sex and mortality was found only in the latter (very elderly) group. Positive relationships of PS ≥2 with mortality was more pronounced in patients ≥80 years of age than in those <80 years of age. A significant positive relationship with non-standard therapy was found only in patients <80 years of age.

Conclusion: PS ≥2 may be positively associated with mortality, regardless of age. Female sex may be inversely related to mortality only in DLBCL patients aged 80 years or more, possibly due to the difference in rituximab clearance between the two study groups.

1. Introduction

In developed countries, the population of elderly patients with cancer is increasing, and how to treat or manage these patients is of major research interest. Despite the increasing prevalence of elderly cancer patients, not many have been enrolled in clinical trials, and limited information is available regarding appropriate cancer chemotherapies for this group. Treatment for these patients is largely provided by non-specialist physicians as part of ongoing general care.

Diffuse large B-cell lymphoma (DLBCL), which is categorized as a non-Hodgkin lymphoma (NHL), is a chemotherapy-sensitive malignancy recognized to be curable with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy.[1,2] However, the majority of clinical trials have focused on patients under 80 years of age,[3,4] which is the average duration of life in developed countries. In addition, recruitment of elderly patients aged 80 years or more into clinical trials is often difficult, so adequate information regarding their treatment is lacking.

In this study, we investigated the relationship between prognostic factors and mortality risk in patients with DLBCL by stratifying the study population into two groups aged <80 and ≥80 years.

* Corresponding author. Department of Clinical Oncology, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan.
E-mail address: yoshiyak@m.ehime-u.ac.jp (Y. Yakushijin).

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2. Material and methods

2.1. Patients

Between January 2006 and December 2013, 202 patients were newly diagnosed by hematopathologists with *de novo* DLBCL at Ehime University Hospital. Pathologic tissue specimens had been collected in addition to routine pathological analysis. We performed gene rearrangement analysis of the immunoglobulin heavy chain (IgH) region using Southern blot or karyotypic analysis along with flow cytometric analysis for CD20 expression on cell surfaces to confirm that the tumours were of B lymphocyte origin. Most of the samples were of lymph nodes, but selected specimens of extranodal (EN) soft tissue were also included. After consideration of past reports, 61 of these 202 patients were deemed as unsuitable cases for the current analysis, as follows: 1) primary DLBCLs of CNS (n = 32 patients)[5]; 2) primary testicular (n = 10), mammary (n = 3) and uterine (n = 2) DLBCLs[6–8]; 3) rheumatoid arthritis- or methotrexate-associated DLBCLs (n = 6)[9]; 4) DLBCLs with concomitant or antecedent follicular lymphoma expressing t(14; 18) (n = 3); 5) DLBCLs associated with HIV infection (n = 2)[10]; 6) B-cell lymphomas, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (n = 1); 7) intravascular large B-cell lymphoma (n = 1)[11]; and 8) primary mammary and methotrexate-associated DLBCL (n = 1). Therefore, the final study group comprised 141 patients. Clinical examination or interview by phone or mail was performed to ascertain the patient survival, physical condition and DLBCL status of all remaining patients. The use of the data of the patients have been regulated by the Ethics Committee for Clinical Studies at Ehime University Graduate School of Medicine (study #1307002), and the consent of the individual patient have not been required.

2.2. Treatments

All patients were treated with R-CHOP (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (maximum 2 mg/body), day 1, and prednisolone 100 mg/body, days 1–5), R-CHOP-like, or other chemotherapy regimens based on their physician's choice. A R-CHOP-like treatment is R-THP-COP therapy (rituximab 375 mg/m^2, cyclophosphamide 750 mg/m^2, pirarubicin 50 mg/m^2, vincristine 1.4 mg/m^2, maximum 2 mg/body, day 1, and prednisolone 100 mg/body, days 1–5). Pirarubicin is an anthracycline drug, which is reported to have the same efficacy as doxorubicin but fewer cardiotoxicities.[12,13] Standard therapy was defined as R-CHOP or R-CHOP-like therapy with over 50% of dose intensity with the dose of the effective drug administered per unit time (mg/m^2/week). Other treatments chosen by the physician were identified as 'non-standard therapy'. Supportive cares and other therapies after chemotherapy were chosen by each physician. Those supportive treatments had not changed from 2006 to 2013, and the study cohort was largely consistent.

2.3. Statistical analysis

Survival time was defined as the interval between the date of enrolment in any treatment and the date of the last follow-up (March 2015) or death. Cox proportional hazard models were used to estimate crude hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality risk relative to the following variables: age (<80 and ≥80 years), sex, stage (≤2 and ≥3), performance status (PS) (≤1 and ≥2), lactate dehydrogenase (LDH) (≤normal limit and >normal limit), extranodal (EN) sites (≤1 and ≥2), modified International Prognostic Index score (*age ≥80*, stage ≥3, PS ≥2, LDH >normal limit, and EN sites ≥2; IPI scoring ≤2 vs. ≥3, which is modified from the original International Prognostic Index (IPI)[14] based on our current concept to identify the elder population-related mortality) and therapy (standard and non-standard). In the multivariate Cox proportional hazard model, we controlled for sex and age; age was used as a continuous confounding variable. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Characteristics of the study patients are shown in Table 1. The mean age of the patients was 71.4 years; 56 (39.7%) of 141 were female; and 83 (58.9%) were alive at the last follow-up. The median duration of follow-up was 32.2 months. At the end of the observation period, age-related survival rates were obtained in Fig. 1(A,B) as Kaplan–Meier survival curves. We analysed the incidences of major treatment-related adverse events such as cardiac, hepatobiliary, and renal disorders. Adverse incidents over grade II toxicities based on CTCAE (Common Terminology Criteria Events) v4.0 did not show any statistical differences between the patients aged 80 years or more (≥80 years of age) and those under 80 years of age (<80 years of age) (data not shown). However, the incidences of febrile neutropenia (FN) in the patients ≥80 years of age during chemotherapies were significantly fewer than in those <80 years of age (3% versus 16%), suggesting that the physicians had a tendency to reduce the dose of chemotherapy agents or not adhere to the standard therapy to avoid infection-associated mortality, especially in the treatment of patients ≥80 years of age.

Table 2 shows hazard ratios (HRs) and the 95% confidence intervals (CIs) for the relationship between selected prognostic factors and mortality risk in the DLBCL patients. Female patients had significantly better survival rates compared to male patients: the age adjusted HR was 0.56 (95% CI: 0.32–0.97). On the other hand, patients ≥80 years of age had a significantly increased risk of death, compared with patients <80 years of age: the sex adjusted HR was 2.68 (95% CI: 1.56–4.61). Similarly, PS (≥2 vs. ≤1), and therapy (non-standard vs. standard) were significantly associated with an increased risk of death: the age and sex adjusted HRs were 3.15 (95% CI: 1.78–5.57), 2.71 (95% CI: 1.60–4.60), and 2.43 (95% CI: 1.34–4.39), respectively. No significant associations were observed between mortality risk and stage, LDL, or EN sites.

When classifying patients by age (<80 and ≥80 years of age), a significant inverse association between female sex and mortality risk was found only in patients aged 80 years or more: the age adjusted HR was 0.35 (95% CI: 0.13–0.94), but the interaction between sex and age with respect to mortality risk was not statistically significant (P for interaction = 0.25) (Table 3). Positive relationship of PS ≥2 with mortality was more pronounced in patients ≥80 years of age than in those <80 years of age. Regarding the relationship with non-standard therapy, a significantly increased risk of death was found only in patients <80 years of age. No significant interactions were observed between age and any of the prognostic factors under study with respect to mortality risk.

4. Discussion

Our current analysis indicated that PS is the strongest prognostic factor for all patient populations with DLBCL. In addition to elderly populations with DLBCL, female sex is inversely correlated with mortality, especially in patients 80 years of age or older, thereby serving as another prognostic factor.

Cancer is more prevalent in the elderly population; more than 50% of cancer diagnoses and deaths are seen in patients older than 65 years, and about 20% of patients with cancer are aged 80 years or

Table 1
Characteristics of study patients.

	Overall (n = 141)	Age group	
		<80 years (n = 108)	≥80 years (n = 33)
Age at diagnosis, years; median (range)	73 (25–94)	69 (25–79)	84 (80–94)
Duration of follow-up period, months; median	32.2	36.5	15.7
Female sex; n (%)	56 (39.7%)	40 (37.0%)	16 (48.5%)
Stage ≥3; n (%)	79 (56.0%)	67 (62.0%)	12 (36.4%)
Performance status ≥2; n (%)	70 (49.7%)	52 (48.2%)	18 (54.6%)
Lactate dehydrogenase > Normal limit; n (%)	84 (59.6%)	66 (61.1%)	18 (54.6%)
Extranodal sites ≥2; n (%)	33 (23.4%)	27 (25.0%)	6 (18.2%)
Modified IPI[a] ≥3; n (%)	55 (39.0%)	42 (38.9%)	13 (39.4%)
Non-standard therapy	34 (24.1%)	13 (12.0%)	21 (63.6%)

[a] Modified IPI (International Prognostic Index): Age ≥80, Stage ≥3, Performance status ≥2, Lactate dehydrogenase >Normal limit, and Extranodal sites ≥2.

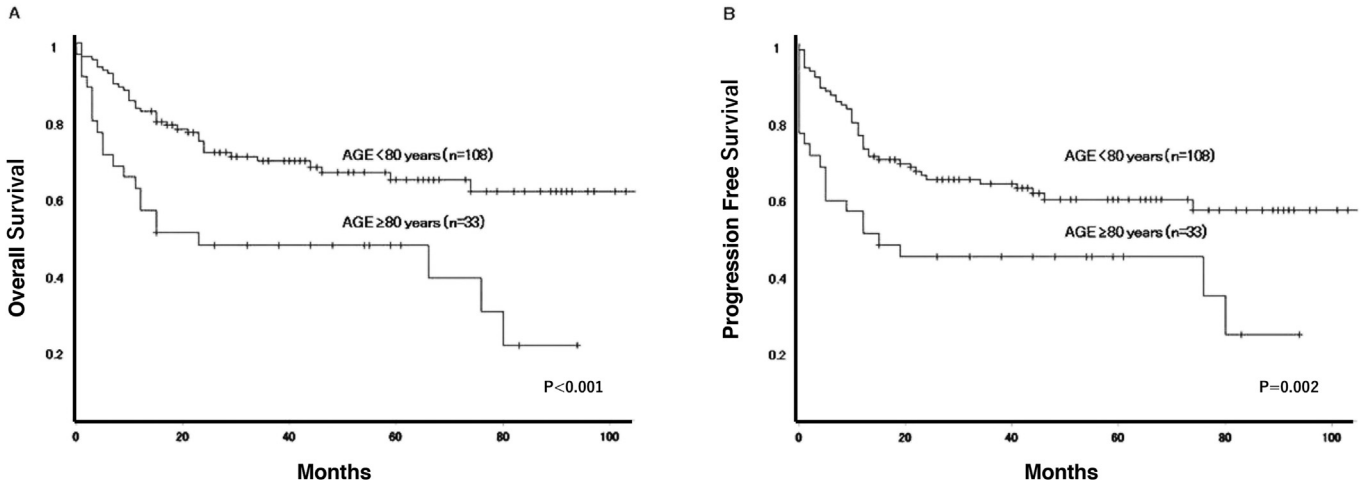

Fig. 1. Figure 1A shows overall survival curves and figure 1B shows progression free survival curves of the patients. Patient prognosis stratified by ≥80 [n = 33] and <80 years [n = 108] of age.

Table 2
Hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality risk in relation to prognostic factors in 141 patients with diffuse large B-cell lymphoma.

		# of events/patients	Univariate HR (95% CI)	Age and sex adjusted HR (95% CI)
Age at diagnosis (years)	<80	37/108	1.00	1.00
	≥80	21/33	2.45 (1.44–4.20)	2.68 (1.56–4.61)
Sex	Male	19/56	1.00	1.00
	Female	39/85	0.62 (0.36–1.08)	0.56 (0.32–0.97)
Stage	≤2	25/62	1.00	1.00
	≥3	33/79	1.13 (0.67–1.90)	1.30 (0.76–2.21)
Performance status	≤1	17/71	1.00	1.00
	≥2	41/70	3.02 (1.72–5.32)	3.15 (1.78–5.57)
Lactate dehydrogenase	≤Normal limit	20/57	1.00	1.00
	>Normal limit	38/84	1.37 (0.79–2.35)	1.65 (0.95–2.86)
Extranodal sites	≤1	42/108	1.00	1.00
	≥2	16/33	1.62 (0.91–2.90)	1.82 (0.99–3.34)
Modified International Prognostic Index[a]	≤2	26/86	1.00	1.00
	≥3	32/55	2.59 (1.54–4.35)	2.71 (1.60–4.60)
Therapy	Standard	34/107	1.00	1.00
	Non-standard	24/31	3.61 (2.13–6.11)	2.43 (1.34–4.39)

[a] Age ≥80, Stage ≥3, Performance status ≥2, Lactate dehydrogenase > Normal limit, and Extranodal sites ≥2.

more.[15] In addition, the incidence of DLBCL, which is the most common type of NHL, is increasing in the elderly, representing approximately 30–45% of all cases of NHL. In population-based cancer registries, the median age at diagnosis is between 70 and 75 years, and approximately 70% of DLBCL occurs in patients more than 65 years old.[15] However, few clinical studies regarding treatment outcomes have focused on elderly patients with DLBCL aged 80 years or more.[16] For instance, two major clinical trials for DLBCL, the Groupe d'Etude des Lymhomes de l'Adulte (GELA) and the RICOVER-60 trials, focused on patients with DLBCL aged from 60 to 61, respectively, to 80 years and were randomized to R-CHOP vs. CHOP or CHOP14 vs. R-CHOP14 chemotherapy.[3,4]

Patients aged 80 years or more are regarded as having survived for more than the average lifespan and the major purpose of treatment for these older cancer patients usually is to maintain their quality of life (QOL), not necessarily to prolong survival. Another reason for the low numbers of clinical trials of these patients is the diminished organ function and increased incidence of

Table 3
Age and sex adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality risk in relation to prognostic factors in patients with diffuse large B-cell lymphoma stratified by age <80 and ≥80 years.

	Age and sex adjusted HR (95% CI)		P for interaction
	<80 years (n = 108)	≥80 years (n = 33)	
Female sex	0.72 (0.36–1.43)	0.35 (0.13–0.94)	0.25
Stage ≥3	1.06 (0.54–2.05)	1.88 (0.76–4.65)	0.22
Performance status ≥2	2.93 (1.44–5.95)	3.90 (1.36–11.2)	0.78
Lactate dehydrogenase >Normal limit	1.52 (0.75–3.07)	1.72 (0.69–4.27)	0.91
Extranodal sites ≥2	1.70 (0.83–3.51)	2.10 (0.65–6.76)	0.65
Modified International Prognostic Index[a] ≥3	2.56 (1.33–4.91)	3.23 (1.22–8.55)	0.77
Non-standard therapy	2.96 (1.34–6.54)	1.74 (0.65–4.67)	0.71

[a] Age ≥80, Stage ≥3, Performance status ≥2, Lactate dehydrogenase > Normal limit, and Extranodal sites ≥2.

complications after chemotherapy (including anthracyclines) seen in this age group. Therefore, treatment and outcomes of the elderly population with DLBCL will depend on individual differences. Age is considered one of the more powerful prognostic factors for DLBCL patients, which is consistent with our current results.

In the present study, we have tried to identify prognostic factors other than age for very elderly patients with DLBCL. Disease progression, including stage and EN involvement, is a strong prognostic factor listed in the International Prognostic Index, and is accepted worldwide as a classical prognostic factor for patients with DLBCL of any age.[14] Nevertheless, neither stage ≥3 nor EN sites ≥2 was significantly related to death in patients aged less than 80 years or in those aged 80 years or more in the current study. Progressive disease status should worsen the PS of cancer patients, and thus PS is an additional prognostic factor in the majority of cancers at any age. When the patients PS worsens, standard chemotherapy with intensive doses should be avoided in the majority of cases to relieve the toxicity and preserve the QOL during treatment. Therefore, non-standard chemotherapy without anthracyclines or less intensive doses should be selected. However, doing so could reduce the cure rate, resulting in the dilemma of providing treatment for the population with worsened PS. Age and PS are strongly linked to the intensity of the effects of chemotherapy in patients of any age. In our study, non-standard therapy (less intensive treatment) was significantly associated with mortality risk in patients less than 80 years of age; however, unexpectedly, non-standard therapy was not related to mortality risk in patients 80 years of age or older (Table 3). Most likely, standard therapy (R-CHOP) and its dose are too toxic for patients aged ≥80. This result indicates that patients should be treated in consideration of therapeutic effect and toxicity. In contrast, a significant inverse association between female sex and mortality risk was found in patients aged 80 years or more but not those aged less than 80 years. Recent clinical and biological analyses of rituximab-containing treatments have indicated that the female sex confers better disease prognosis than the male sex, not only for lymphoid malignancies,[17–21] but also for benign diseases.[22] Recent retrospective analyses based on the RICOVER-60 study[4] have shown that elderly women have significantly slower rituximab clearance compared with elderly men,[18,23] suggesting that higher and longer exposure to rituximab during treatment may result in the better prognosis seen in female patients with DLBCL. This is similar to that seen in the prolonged treatment for follicular lymphoma.[17,24,25] Results from these studies might explain why non-standard therapy was not a significant prognostic factor in the very elderly population of the current study. The majority of our patients aged 80 years or more (n = 21) in the non-standard therapy group were still treated with rituximab-combined chemotherapy. In other words, the strong prognostic impact for very elderly patients, especially women, may support decisions for the use of rituximab.

Regarding the treatment for elderly patients, there is a necessity to provide optimal treatment from all points of view. Elderly patients with DLBCL still do not have a standard treatment regimen, and we should keep in mind that the lack of a standard therapy might attenuate cure possibilities among elder patients. Therefore, careful evaluation of not only age, but also of PS and organ function, self-discipline, and the support of family members must be performed in addition to detailed pathological examinations, in order to design optimal treatment strategies. Individualized, insightful support by the medical care team is also essential. Recently, the International Society of Geriatric Oncology (ISGO) has proposed the Comprehensive Geriatric Assessment (CGA) as a multidisciplinary evaluation tool for elderly patients with cancer[26–28] and several groups have reported its efficacy in the treatment of DLBCL. CGA consists of an evaluation of overall status and the physical abilities of patients, and its use perhaps would reflect our current prognostic factors for DLBCL patients aged 80 years or more. We need more biological factors to predict patient outcomes.

The present study had methodological advantages in that all suitable patients diagnosed with DLBCL in Ehime University Hospital between January 2006 and December 2013 were included and that the relationships between prognostic factors and mortality risk were assessed among the 33 patients aged 80 years or more. Several methodologic weaknesses of the present study have to be taken into account. We did not control for confounding factors other than age and sex, and the number of study subjects was small; however, significant associations were detected.

5. Conclusion

The present study in Japan suggests that PS ≥2, and non-standard therapy may be positively related to death in patients with DLBCL aged less than 80 years, and that PS ≥2 may be positively associated with mortality, while female sex may be inversely related to mortality in those aged 80 years or more. We acknowledge that the current results must be confirmed by additional epidemiologic studies with a larger sample size.

Conflict of interests

The authors have no conflict of interest to declare.

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