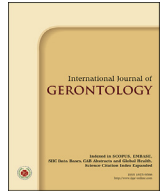




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Original Article

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.

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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/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² (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/m², cyclophosphamide 750 mg/m², pirarubicin 50 mg/m², vincristine 1.4 mg/m², 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/m²/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

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