Use of benzodiazepines is the risk factor for infection in patients aged 80 years or older with diffuse large B-cell lymphoma: A single-institution retrospective study

Anna Ogiso, Tomohiro Mizuno, Kaori Ito, Fumihiro Mizokami, Akihiro Tomita, Shigeki Yamada

1 Department of Clinical Pharmacy, Fujita Health University School of Medicine, Toyoake, Japan, 2 Department of Hematology, Fujita Health University School of Medicine, Toyoake, Japan, 3 Department of Pharmacy, National Center for Geriatrics and Gerontology, Obu, Japan

☯ These authors contributed equally to this work.
* tomohiro.mizuno@fujita-hu.ac.jp

Abstract

Background

The number of patients aged 80 years or older with diffuse large B-cell lymphoma (DLBCL) is increasing, and the incidence rate of the disease in this population group reaches up to 20%. The risk of infection is higher in older patients than in other patients. Although hypnotic drugs are frequently detected as potentially inappropriate medications, it is unclear whether hypnotic drugs affect the occurrence of infection during chemotherapy. Here, we investigated whether the use of hypnotic drugs is associated with infection during first-line chemotherapy in patients with diffuse large B-cell lymphoma (DLBCL) aged 80 years or older.

Methods

Japanese patients aged 80 years or older with diffuse large B-cell lymphoma who had received first-line chemotherapy at Fujita Health University Hospital from January 2005 to March 2020 were enrolled in this retrospective cohort study. The primary study outcome was the identification of the risk factor for infection during first-line chemotherapy.

Results

This study included 65 patients received first-line chemotherapy. The proportion of patients with National Comprehensive Cancer Network-international prognostic index ≥ 6 was higher in the infection group than in the non-infection group. The relative dose intensity of each anticancer drug (cyclophosphamide, Adriamycin, and vincristine) and dose of prednisolone did not significantly differ between the two groups. Multivariate analysis showed that the use of benzodiazepines was a risk factor for infection (odds ratio, 4.131 [95% confidence interval: 1.225–13.94], P = 0.022).
Conclusion

DLBCL patients using benzodiazepines should be monitored for infection symptoms during chemotherapy.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent type in non-Hodgkin lymphoma (NHL) [1, 2]. In Japan, DLBCL has been reported to account for 45.3% of all cases of NHL [3]. The number of patients aged 80 years or older with DLBCL is increasing [4], and the frequency of those patients reaches approximately 20% [3]. Older patients with DLBCL show variable degrees of functional impairment, comorbidity, chronic undernutrition, and altered drug metabolism [5, 6]. Therefore, the risk of adverse drug reactions is higher in older patients than in other patients. To improve treatment outcomes and avoid severe adverse drug reactions, the type of chemotherapeutic regimen and dose intensity are determined considering the National Comprehensive Cancer Network (NCCN)-international prognostic index (IPI) for the prediction of outcomes in patients with aggressive lymphoma [7]. The NCCN-IPI helps predict mortality in patients with DLBCL by using age, lactate dehydrogenase (LDH) levels, Ann Arbor stage, and Eastern Cooperative Oncology Group performance status (PS). Although the NCCN-IPI is a good predictor of mortality, it remains unclear whether it can be a predictor of adverse drug reactions during chemotherapy.

An infectious episode is a well-known adverse drug reaction and has been reported to be associated with increased mortality [8, 9]. Comorbidity is reported as an independent risk factor for severe adverse drug reactions [10]. In addition, older age [11] and rituximab (R)-based chemotherapy [12] increase the risk of infection. Patients aged 75 years or older are classified as the group with the highest risk of poor prognoses per the NCCN-IPI and account for 40.8% of all patients with DLBCL [3]. Thus, the identification of risk factors for infection might improve clinical outcomes in such older patients (e.g., patients aged 80 years or older).

Inappropriate medication use and drug interactions are resulting from poor functional impairment in older patients. Several screening tools are available to evaluate the appropriateness of pharmacotherapy for older patients and to avoid inappropriate medication use and drug interactions. Although these tools have shown that hypnotic drugs increase the risk for falls or fractures [13, 14], it is unclear whether hypnotic drugs influence the occurrence of infection during chemotherapy. Hence, in this study, we investigated whether the use of hypnotic drugs is associated with infection during first-line chemotherapy in patients aged 80 years or older.

Materials and methods

Study design and data source

Japanese patients aged 80 years or older with DLBCL who had received first-line chemotherapy at Fujita Health University Hospital from January 2005 to March 2020 were enrolled in this retrospective cohort study. All medical data were collected from the hospital’s medical records. The exclusion criteria were as follows: (a) patients whose baseline data were unavailable and (b) patients without completed first-line chemotherapy. The standard chemotherapy regimens used were R-CHOP (a combination of R, cyclophosphamide [CPA], adriamycin [ADR], vincristine [VCR], and prednisolone [PSL]), CHOP (a combination of CPA, ADR, VCR, and
PSL), COP (a combination of CPA, VCR, and PSL), R-COP (a combination of R, CPA, VCR, and PSL), CHP (a combination of CPA, ADR, and PSL), R-CHP (a combination of R, CPA, ADR, and PSL), and R-HOP (a combination of R, ADR, VCR, and PSL). The RDI was calculated by dividing the DI of each chemotherapeutic drug (R, CPA, ADR, and VCR) by the respective target DI and multiplying by 100 [15]. Disorders were categorized according to the modified Charlson Comorbidity Index (CCI) [6, 16].

Outcome measures
The identification of the risk factors for infection during first-line chemotherapy was the primary outcome of this study. Infection severity was defined in terms of grade 2 or higher based on the Common Terminology Criteria for Adverse Events version 5.0, as follows:
• Grade 2: Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)
• Grade 3: IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated
• Grade 4: Life-threatening consequences; urgent intervention indicated
• Grade 5: Death

Patients received administration of prophylactic antibiotics were not defined as CTCAE grade 2.

The NCCN-IPI was determined as described in a previous report [7]. Briefly, age, lactate dehydrogenase ratio (ratio to the institutional upper limit of normal), Ann Arbor stage, the presence of extranodal disease, and PS were used to determine the NCCN-IPI.

Statistical analyses
All data are shown as medians and ranges. The Mann–Whitney U test was used for comparisons of data without normal distribution. The chi-square test and Fisher’s exact test were used to analyze nominal scales. Logistic regression analysis using a multivariable model was performed to identify the risk factors for the infection events. To determine the risk factors for infection, logistic regression analysis with a multivariable model was applied for the following covariates: NCCN-IPI and benzodiazepine use. To avoid multicollinearity with the NCCN-IPI, PS was not included in the multivariate analysis. The fitness of the logistic regression model was evaluated using the Hosmer–Lemeshow test. The predictive ability was evaluated by plotting the receiver operating characteristic curve. A two-sided P-value of <0.05 was considered significant in all statistical analyses, which were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA).

Ethics approval
This study was approved by the ethics board of Fujita Health University Hospital (ethics committee approval number: HM21-205) and conducted according to the appropriate guidelines. Because this was a retrospective cohort study, an opt-out approach for informed consent was used according to the approval of the ethics board.

Results
Patient characteristics
This study included 65 patients who had received first-line chemotherapy at Fujita Health University Hospital (Fig 1). The baseline characteristics of the subjects are shown in Table 1. The
median age was 83 years in the all subjects. The CCI for each patient ranged from 2 to 9. Patients with or without infection events were divided into non-infection (n = 46) and infection (n = 19) groups, respectively. The PS in the infection group was significantly higher than that in the non-infection group (P = 0.049). The proportion of patients with NCCN-IPI of ≥6 was higher in the infection group than in the non-infection group (P = 0.053). The RDI of each drug (R, CPA, ADR, and VCR) and PSL dose were not significantly different between the two groups. Furthermore, the number of concomitant medications was not significantly different between the groups (Table 1), and the types of concomitant medications were similar in the two groups (Table 2). However, the proportion of patients using benzodiazepines was higher in the infection group than in the non-infection group (Table 2).

**Risk factors for infection**

The results of univariate and multivariate analyses are shown in Table 3. The univariate analysis revealed that poor PS and the use of benzodiazepines were significant risk factors for infection (PS ≥ 2, OR = 3.055 [95% CI: 0.945–9.877], P = 0.056; NCCN-IPI ≥ 6, OR = 2.924 [95% CI: 0.966–8.855], P = 0.053; use of benzodiazepines, OR = 4.275 [95% CI: 1.314–13.91], P = 0.027). Meanwhile, extranodal disease, bone marrow infiltration, central nervous system infiltration, advanced cancer, CCI, polypharmacy, and the use of antulcer drug were not associated with infection events. NCCN-IPI affects clinical outcomes more than PS, and these are confounding factors. Therefore, we performed multivariate analysis using NCCN-IPI and use of benzodiazepines. The use of benzodiazepines was identified as a risk factor for infection in multivariate analysis (OR = 4.131 [95% CI: 1.225–13.94], P = 0.022). To determine whether the use of benzodiazepines is a predictor of the occurrence of infection, we evaluated the predictive ability by using receiver operating characteristic curve analysis. The use of benzodiazepines showed a trend toward good prediction of the occurrence of infection (sensitivity, 0.474; specificity, 0.826; AUC, 0.650 [95% CI, 0.495–0.805], P = 0.059) (Fig 2).
Types of infections

Types of infections and pathogens are shown in Table 4. The presence of infection was determined by hematology clinicians. Based on the Common Terminology Criteria for Adverse Events version 5.0 grade of infection, any use of oral or IV antibiotics was considered infection. Febrile neutropenia was the most frequent infection (26.3%, n = 5), followed by the common

Table 1. Baseline characteristics.

| Baseline Characteristics | Total (n = 65) | Infection group (n = 19) | Non-infection group (n = 46) | P value |
|--------------------------|---------------|--------------------------|-----------------------------|---------|
| Age, yrs (range)         | 83.0 (80–91)  | 82.5 (80–90)             | 83.0 (80–91)                | 0.550   |
| Male, no (%)             | 23 (35.4)     | 6 (31.6)                 | 17 (37.0)                   | 0.780*  |
| Body surface area (range)| 1.43 (1.06–1.67) | 1.45 (1.06–1.66) | 1.43 (1.15–1.67) | 0.988   |
| Body mass index (range)  | 20.4 (15.5–33.4) | 21.5 (16.4–31.0) | 20.3 (15.5–33.4) | 0.306   |
| Performance status (range)| 2 (0–4)     | 2 (1–4)                  | 1 (0–4)                     | 0.049   |
| ≥ 2, no (%)              | 36 (55.4)     | 14 (73.7)                | 22 (47.8)                   | 0.056b  |
| Extranodal disease, no (%) | 23 (35.4) | 7 (36.6)                | 16 (34.8)                   | 1.000*  |
| Bone marrow infiltration, no (%) | 9 (13.8) | 2 (10.5)                 | 7 (15.2)                    | 1.000*  |
| Central nervous system infiltration, no (%) | 1 (1.53) | 1 (5.26)                 | 0 (0)                       | 0.292*  |
| Ann Arbor stage III-IV, no (%) | 35 (53.8) | 12 (63.2)                | 24 (52.2)                   | 0.418b  |
| Number of neutrophil, 10^3/μL (range) | 3.85 (0.28–125) | 4.08 (2.77–12.5) | 3.74 (0.28–10.9) | 0.289   |
| Number of platelet, 10^4/μL (range) | 19.9 (3.4–43.8) | 19.6 (3.4–32.2) | 20.1 (10.1–43.8) | 0.466   |
| Albunin, g/dL (range)    | 3.4 (1.8–5.2) | 3.5 (1.8–4.1)            | 3.4 (2.1–5.2)               | 0.795   |
| LDH ratio (range)        | 1.14 (0.60–13.6) | 1.41 (0.73–13.5) | 1.11 (0.60–4.84) | 0.489   |
| 0, no (%)                | 26 (40.0)     | 7 (36.8)                 | 19 (41.3)                   | 0.433b  |
| 1, no (%)                | 31 (47.7)     | 10 (52.6)                | 21 (45.7)                   |         |
| 2, no (%)                | 8 (12.3)      | 2 (10.5)                 | 6 (13.0)                    |         |
| NCCN-IPI                 | 5 (3–8)       | 6 (3–7)                  | 5 (3–8)                     | 0.219   |
| ≥ 6, no (%)              | 29 (44.6)     | 12 (63.2)                | 17 (37.0)                   | 0.053b  |
| CCI                      | 3 (2–9)       | 2 (2–4)                  | 3 (2–9)                     | 0.245   |
| ≥ 3, no (%)              | 34 (52.3)     | 8 (42.1)                 | 26 (56.5)                   | 0.413b  |
| Number of concomitant medications | 5 (0–15) | 7 (0–12) | 5 (0–15) | 0.417 |
| ≥ 6 medications, no (%) | 29 (44.6) | 11 (57.9) | 18 (39.1) | 0.166b |

Chemotherapy regimen and RDI

| R-CHOP, no (%) | 21 (32.3) | 9 (47.4) | 12 (26.1) | 0.642b |
| CHOP, no (%)    | 27 (41.5) | 6 (31.6) | 21 (45.7) |         |
| COP, no (%)     | 5 (7.69)  | 2 (10.5) | 3 (6.52)  |         |
| R-COP, no (%)   | 9 (13.8)  | 2 (10.5) | 7 (15.2)  |         |
| CHP, no (%)     | 1 (1.54)  | 0 (0.00) | 1 (2.17)  |         |
| R-CHP, no (%)   | 1 (1.54)  | 0 (0.00) | 1 (2.17)  |         |
| R-HOP, no (%)   | 1 (1.54)  | 0 (0.00) | 1 (2.17)  |         |
| Rituximab RDI, % (range) | 98.4 (0–106) | 97.5 (0–105) | 99.2 (0–106) | 0.264 |
| Cyclophosphamide RDI, % (range) | 69.2 (0–83.3) | 65.2 (49.5–80.3) | 68.5 (0–83.3) | 0.863 |
| Doxorubicin RDI, % (range) | 59.9 (0–83.3) | 61.3 (67.7–77.7) | 59.6 (0–83.3) | 0.873 |
| Vincristine RDI, % (range) | 68.4 (0–97.1) | 66.9 (42.9–71.7) | 68.4 (0–97.1) | 0.920 |
| Prednisolone, mg (range) | 50 (0–100) | 50 (0–60) | 52 (0–100) | 0.188 |

CCI: Charlson Comorbidity Index, LDH: lactate dehydrogenase, NCCN-IPI: National Comprehensive Cancer Network-international prognostic index, R: rituximab, C: cyclophosphamide, H: adriamycin, O: vincristine, P: prednisolone, RDI: relative dose intensity,

*Fisher’s exact test,

b chi-square test

https://doi.org/10.1371/journal.pone.0269362.t001

PLOS ONE | https://doi.org/10.1371/journal.pone.0269362 June 10, 2022 5 / 11
cold (15.7%, n = 3). Five patients (26.3%) in the infection group had oral (gingival lesion, periodontitis) and gastrointestinal (including bile duct) infections.

**Discussion**

This study was aimed at investigating whether the use of hypnotic drugs is associated with infection during first-line chemotherapy in patients with DLBCL aged 80 years or older. Our results suggested that compared to a high NCCN-IPI, the use of benzodiazepines was potentially associated with infection events during chemotherapy. Although dose intensity is related to mortality in patients with DLBCL [17], it was not identified as a risk factor for infection in our study.

Older patients are at a higher risk of infection-related mortality than are younger patients [18–20]. To decrease treatment-related mortality, risk factors and optimal dose intensity were assessed in older patients. Dose modification has been reported as a strategy for improving therapeutic outcomes [21]; however, the optimal dose for older patients with DLBCL remains unclear [22]. Although the determination of the optimal dose might decrease the risk of adverse drug events (including infection), RDI did not differ between the infection and non-infection groups in the present study. We could not conclude whether dose intensity affects

| Types of concomitant medications | Infection group (n = 19) | Non-infection group (n = 46) | P value |
|----------------------------------|-------------------------|-----------------------------|---------|
| Antihypertensive drugs (n) (%)   | 15 (78.9)               | 29 (63.0)                   | 0.212<sup>b</sup> |
| Antidiabetic drug (n) (%)        | 0 (0)                   | 6 (13.0)                    | 0.169<sup>a</sup> |
| Lipid-lowering drugs (n) (%)     | 7 (36.8)                | 17 (37.0)                   | 1.000<sup>a</sup> |
| Anticoagulant or antiplatelet drugs (n) (%) | 6 (31.6)               | 15 (32.6)                   | 1.000<sup>a</sup> |
| Antiulcer drug (n) (%)           | 9 (47.4)                | 19 (41.3)                   | 0.784<sup>a</sup> |
| Hypnotic drug (n) (%)            | 10 (52.6)               | 8 (17.4)                    | 0.006<sup>a</sup> |
| Benzodiazepines (n) (%)          | 9 (47.3)                | 8 (17.4)                    | 0.027<sup>a</sup> |
| Anti-osteoporosis drug (n) (%)   | 3 (15.8)                | 10 (21.7)                   | 0.740<sup>a</sup> |

<sup>a</sup>Fisher’s exact test,
<sup>b</sup>chi-square test

https://doi.org/10.1371/journal.pone.029362.1002

| Characteristics                     | Univariate analysis | P value | Multivariate analysis | P value |
|-------------------------------------|---------------------|---------|-----------------------|---------|
|                                     | OR (95%CI)          |         | OR (95%CI)            |         |
| PS ≥ 2                              | 3.055 (0.945–9.877) | 0.056   | 2.811 (0.881–8.969)   | 0.081   |
| Extraneural disease                 | 1.094 (0.360–3.326) | 1.000   | 1.000                 | 1.000   |
| Bone marrow infiltration            | 0.655 (0.123–3.487) | 1.000   | 1.000                 | 1.000   |
| Central nervous system infiltration | 1.056 (0.949–1.174) | 0.292   | 1.000                 | 1.000   |
| Ann Arbor stage III-IV              | 1.571 (0.525–4.707) | 0.418   | 1.000                 | 1.000   |
| NCCN-IPI ≥ 6                        | 2.924 (0.966–8.855) | 0.053   | 2.811 (0.881–8.969)   | 0.081   |
| CCI ≥ 3                            | 0.559 (0.190–1.650) | 0.413   | 1.000                 | 1.000   |
| Number of concomitant medication ≥ 6| 2.139 (0.722–6.338) | 0.166   | 1.000                 | 1.000   |
| Antihyperglycemic drug              | 1.279 (0.437–3.747) | 0.784   | 1.000                 | 1.000   |
| Benzodiazepine use                  | 4.275 (1.314–13.91) | 0.027   | 4.131 (1.225–13.94)   | 0.022   |

OR: odds ratio; CI: confidence interval.

https://doi.org/10.1371/journal.pone.029362.1003
the occurrence of infections in the present study, and PS and the proportion of patients with a high NCCN-IPI were high in the infection group. A previous study showed that the proportion of infectious events was higher in a very high-risk age group (age: 60–75 years with PS = 4 or age >75 years) than that of in a standard-risk age group (age: 60–75 years with PS = ≤3 or age <60 years) groups [23]. The study revealed that multiple risk factors should be evaluated to prevent infectious events; however, the information on concomitant medications was limited. Therefore, we assessed whether NCCN-IPI and concomitant medications could be a risk factor for infection, and found that concomitant medications were associated with the occurrence of infection during chemotherapy in patients with DLBCL.

The occurrence rate of treatment-related adverse drug events in chemotherapy is higher than that associated with other treatments. In patients with metastatic cancer, high PS and

Table 4. Types of infections and pathogen.

| Types of Infections                        | Pathogen (n)     | No (%) |
|-------------------------------------------|------------------|-------|
| Febrile neutropenia                       | Unknown(5)       | 5 (26.3) |
| Elevated C-reactive protein level and having common cold symptoms | Unknown(3)    | 3 (15.7) |
| Bacterial septicemia                      | *Escherichia coli*(1) | 2 (10.5) |  
|                                           | MRSE(1)          |       |
| Infection from gastrointestinal tract lesion | *Enterococcus sp.*(1) | 2 (10.5) |
|                                           | Unknown(1)       |       |
| CRBSI                                     | Unknown (1)      | 1 (5.2) |
| Cholangitis                               | *Enterococcus faecium* (1) | 1 (5.2) |
| Urinary tract infection                   | Unknown(1)       | 1 (5.2) |
| Infection from gingival lesion            | *Corynebacterium sp*(1) | 1 (5.2) |
| Herpes simplex                            | Herpes simplex virus type 1 (1) | 1 (5.2) |
| Periodontitis                             | Unknown(1)       | 1 (5.2) |
| Infection from skin inflammation          | MSSA (1)         | 1 (5.2) |

CRBSI: catheter-related blood stream infection  
MRSE: Methicillin-Resistant *Staphylococcus epidermidis*  
MSSA: meticillin-susceptible *S. aureus*

https://doi.org/10.1371/journal.pone.0269362.t004
polypharmacy are risk factors for hospitalization or an emergency room visit [24]. Therefore, it is necessary to assess the risk of polypharmacy in patients with cancer. Our results suggested that the number of concomitant medications was not associated with the occurrence of infection during chemotherapy. Since the number of concomitant medications is associated with comorbidity, we assessed the state of comorbidity by using CCI. Although a high CCI has been reported to be a risk factor for mortality in patients with DLBCL [10, 25], it was not the risk factor for infection events in our study. Interestingly, the use of benzodiazepines was found to be a risk factor for infection.

Two major screening tools recommended that older adults should avoid the use of benzodiazepines [26, 27]. The peripheral benzodiazepine receptor is expressed in immune cells, and benzodiazepines have several effects on the immune system [28–31]. Diazepam serves as an immunomodulator, controlling undesired innate and adaptive immune responses [32]; furthermore, it has a notable suppressive effect on immune surveillance [33]. Additionally, sedative drug use results in impaired clearing of oral secretions because it inhibits the swallowing of saliva [34]. Further, relaxation of the lower esophageal sphincter by benzodiazepines might increase reflux events [35]. In the current study, the frequency of oral and gastrointestinal infection was higher than that of other infection sites, and the frequency of using antulcer drugs in infection group was higher than that in the non-infection group. Thus, our results suggest that the impairment of oral secretions and the relaxation of the lower esophageal sphincter were associated with infections events. The patients with benzodiazepine use in our study had a low body surface area (S1 Table). Because sleep disorder is associated with a low skeletal muscle mass and poor physical performance [36], it was possibility that sarcopenia affected the immune system. Since we did not assess oral secretions, reflux events, and skeletal muscle mass, these are speculations for the mechanism of benzodiazepine-induced infection. However, benzodiazepine use might be a factor to consider for the occurrence of infection during chemotherapy in older patients with DLBCL.

Our study has several limitations. First, this was a single-center and retrospective study. The number of subjects and clinical parameters evaluated in our study were limited. To verify our results, the multicenter research and a large spontaneous reporting system (e.g., Japanese Adverse Drug Event Report database, FDA Adverse Event Reporting System) might be useful in the further study. Second, the patients received different chemotherapy regimens (i.e., R-CHOP, CHOP, and COP). Although the proportions of patients who received each of the chemotherapy regimens were not significantly different between the infection and non-infection groups, further studies should enroll patients who received the same chemotherapy regimen. Third, we could not come to a conclusion about the mechanism of benzodiazepine-induced infection. Oral secretions, reflux events, and skeletal muscle mass should be evaluated in further studies.

In conclusion, patients with DLBCL using benzodiazepines should be monitored for infection symptoms during chemotherapy.

Supporting information

S1 Table. Baseline characteristics of the patients in the benzodiazepines and non-benzodiazepines groups. CCI: Charlson Comorbidity Index, LDH: lactate dehydrogenase, NCCN-IPI: National Comprehensive Cancer Network-International Prognostic Index, R: rituximab, C: cyclophosphamide, H: adriamycin, O: vincristine, P: prednisolone, RDI: relative dose intensity, aFisher’s exact test, bchi-square test. (DOCX)
S1 Raw data.
(XLSX)

Acknowledgments
We would like to thank Editage (https://www.editage.com/) for editing and reviewing the manuscript for language.

Author Contributions

Conceptualization: Anna Ogiso, Tomohiro Mizuno, Kaori Ito, Fumihiro Mizokami.

Data curation: Anna Ogiso, Kaori Ito.

Formal analysis: Anna Ogiso.

Investigation: Anna Ogiso.

Methodology: Anna Ogiso, Tomohiro Mizuno.

Project administration: Tomohiro Mizuno, Shigeki Yamada.

Supervision: Shigeki Yamada.

Writing – original draft: Anna Ogiso, Tomohiro Mizuno, Kaori Ito, Fumihiro Mizokami, Akihiro Tomita.

References

1. Flowers CR, Sinha R, Vose JM. Improving outcomes for patients with diffuse large B-cell lymphoma. CA Cancer J Clin. 2010; 60(6):393–408. Epub 2010/10/30. https://doi.org/10.3322/caac.20087 PMID: 21030533.

2. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016; 127(20):2375–90. Epub 2016/03/17. https://doi.org/10.1182/blood-2016-01-643569 PMID: 26980727.

3. Tsutsue S, Tobinai K, Yi J, Crawford B. Nationwide claims database analysis of treatment patterns, costs and survival of Japanese patients with diffuse large B-cell lymphoma. PLoS One. 2020; 15(8):e0237509. Epub 2020/08/19. https://doi.org/10.1371/journal.pone.0237509 PMID: 32810157 Health Japan.

4. Tajima K, Takahashi N, Ishizawa K, Murai K, Akagi T, Noji H, et al. Clinicopathological characteristics of malignant lymphoma in patients with hepatitis C virus infection in the Tohoku district in Eastern Japan. Leuk Lymphoma. 2017; 58(6):1509–11. Epub 2016/10/12. https://doi.org/10.1080/10428194.2016.1236376 PMID: 27724155.

5. Ribera JM. Hope for very elderly patients with diffuse large B-cell lymphoma. Lancet Oncol. 2011; 12(5):412–3. Epub 2011/04/13. https://doi.org/10.1016/S1470-2045(11)70080-8 PMID: 21482185.

6. Fields PA, Linch DC. Treatment of the elderly patient with diffuse large B cell lymphoma. Br J Haematol. 2012; 157(2):159–70. Epub 2012/04/03. https://doi.org/10.1111/j.1365-2411.2011.09011.x PMID: 22463486.

7. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. Blood. 2014; 123(6):837–42. Epub 2013/11/23. https://doi.org/10.1182/blood-2013-09-524108 PMID: 24264230.

8. Dendle C, Gilbertson M, Spelman T, Stuart RL, Korman TM, Thursky K, et al. Infection is an Independent Predictor of Death in Diffuse Large B Cell Lymphoma. Sci Rep. 2017; 7(1):4395. Epub 2017/07/02. https://doi.org/10.1038/s41598-017-04495-x PMID: 28667319 study but had no part in the design, conduct, analysis or preparation of the manuscript. S.O. has received speakers fees and clinical research funding from Roche. M.G., T.S., Z.M., R.S. and T.K. declare no potential conflict of interest.

9. Asano K, Yamashita Y, Ono T, Natsumeda M, Beppu T, Matsuda K, et al. The Real-World status and risk factors for a poor prognosis in elderly patients with primary central nervous system malignant lymphomas: a multicenter, retrospective cohort study of the Tohoku Brain Tumor Study Group. Int J Clin Oncol. 2021. Epub 2021/10/13. https://doi.org/10.1007/s10147-021-02042-3 PMID: 34637053.
10. Wieringa A, Boslooper K, Hoogendoorn M, Joosten P, Beeren T, Storm H, et al. Comorbidity is an independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: a population-based cohort study. Br J Haematol. 2014; 165(4):489–96. Epub 2014/04/24. https://doi.org/10.1111/bjh.12765 PMID: 24754632.

11. Aapro MS, Bohlius J, Cameron DA, Dal Lago L, Donnelly JP, Kearney N, et al. 2010 update of EORTC guidelines for the use of granulocyte-colony stimulating factor to reduce the incidence of chemotherapy-induced febrile neutropenia in adult patients with lymphoproliferative disorders and solid tumours. Eur J Cancer. 2011; 47(1):8–32. Epub 2010/11/26. https://doi.org/10.1016/j.ejca.2010.10.013 PMID: 21095116.

12. Lanini S, Molloy AC, Fine PE, Prentice AG, Ippolito G, Kibbler CC. Risk of infection in patients with lymphoma receiving rituximab: systematic review and meta-analysis. BMC Med. 2011; 9:36. Epub 2011/04/13. https://doi.org/10.1186/1741-7015-9-36 PMID: 21481281.

13. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019; 67(4):674–94. Epub 2019/01/30. https://doi.org/10.1111/jgs.15767 PMID: 30693946.

14. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person’s Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). Consensus validation. Int J Clin Pharmacol Ther. 2008; 46(2):72–83. Epub 2008/01/26. https://doi.org/10.5414/cpp46072 PMID: 18218287.

15. Lee S, Fujita K, Morishita T, Oiwa K, Tsukasaki H, Negro E, et al. Association of the Geriatric 8 with independent prognostic factor in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP: the Intergroup experience (CALGB 9793; ECOG-SWOG 4494). Leuk Lymphoma. 2017; 58(8):1814–22. Epub 2016/12/15. https://doi.org/10.1080/10428194.2016.1265111 PMID: 27967294.

16. Długosz-Danecka M, Szmit S, Ogórka T, Skotnicki AB, Jurczak W. The average relative dose intensity of R-CHOP is an independent factor determining favorable overall survival in diffuse large B-cell lymphoma patients. Cancer Med. 2019; 8(3):1103–9. Epub 2019/02/12. https://doi.org/10.1002/cam4.2008 PMID: 30740919.

17. Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, et al. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunotherapy era. Cancer. 2017; 123(17):3326–34. Epub 2017/05/04. https://doi.org/10.1002/cncr.30739 PMID: 28464214.

18. Lugtenburg P, Silvestre AS, Rossi FG, Noens L, Krall W, Bendall K, et al. Impact of age group on febrile neutropenia risk assessment and management in patients with diffuse large B-cell lymphoma treated with R-CHOP regimens. Clin Lymphoma Myeloma Leuk. 2012; 12(5):297–305. Epub 2012/10/09. https://doi.org/10.1016/j.clml.2012.06.004 PMID: 23040435.

19. Morrison VA, Weller EA, Habermann TM, Li S, Fisher RI, Cheson BD, et al. Patterns of growth factor usage and febrile neutropenia among older patients with diffuse large B-cell non-Hodgkin lymphoma treated with CHOP or R-CHOP: the Intergroup experience (CALGB 9793; ECOG-SWOG 4494). Leuk Lymphoma. 2017; 58(8):1814–22. Epub 2016/12/15. https://doi.org/10.1080/10428194.2016.1265111 PMID: 27967294.

20. Matsuda S, Suzuki R, Takahashi T, Suehiro Y, Tomita N, Izutsu K, et al. Dose-adjusted EPOCH with or without rituximab for aggressive lymphoma patients: real world data. Int J Hematol. 2020; 112(6):807–16. Epub 2020/09/04. https://doi.org/10.1007/s12185-020-02984-w PMID: 32880824.

21. Vidal L, Lando S, Vaxman I, Shochat T, Raanani P, Gurion R, et al. The effect of R-CHOP dose reduction on overall survival of elderly patients with DLBCL—comparative study. Leuk Lymphoma. 2018; 59(4):904–10. Epub 2017/08/23. https://doi.org/10.1080/10428194.2017.1365856 PMID: 28828883.

22. Tholstrup D, de Nully Brown P, Jurlander J, Hansen M. Feasibility, efficacy and safety of CHOP-14 in elderly patients with very high-risk diffuse large B-cell lymphoma. Br J Haematol. 2014; 165(4):489–96. Epub 2014/04/24. https://doi.org/10.1111/bjh.12765 PMID: 24754632.

23. Hong S, Lee JH, Chun EK, Kim KI, Kim JW, Kim SH, et al. Polypharmacy, Inappropriate Medication Use, and Drug Interactions in Older Korean Patients with Cancer Receiving First-Line Palliative Chemotherapy. Oncologist. 2020; 25(3):e502–e11. Epub 2020/03/13. https://doi.org/10.1634/theoncologist.2019-0085 PMID: 32162799.

24. Lee S, Fujita K, Morishita T, Negro E, Oiwa K, Tsukasaki H, et al. Prognostic utility of a geriatric nutritional risk index in combination with a comorbidity index in elderly patients with diffuse large B-cell lymphoma. Br J Haematol. 2021; 192(1):100–9. Epub 2020/05/16. https://doi.org/10.1111/bjh.16743 PMID: 32410224.
26. Motter FR, Fritzen JS, Hilmer SN, Paniz É V, Paniz VMV. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. Eur J Clin Pharmacol. 2018; 74(6):679–700. Epub 2018/03/29. https://doi.org/10.1007/s00228-018-2446-0 PMID: 29589066.

27. Fulone I, Lopes LC. Potentially inappropriate prescriptions for elderly people taking antidepressant: comparative tools. BMC Geriatr. 2017; 17(1):278. Epub 2017/12/05. https://doi.org/10.1186/s12877-017-0674-2 PMID: 29197326.

28. Ramirez K, Niraula A, Sheridan JF. GABAergic modulation with classical benzodiazepines prevent stress-induced neuro-immune dysregulation and behavioral alterations. Brain Behav Immun. 2016; 51:154–68. Epub 2015/09/08. https://doi.org/10.1016/j.bbi.2015.08.011 PMID: 26342944.

29. Taupin V, Jayais P, Descamps-Latscha B, Cazalaa JB, Barrier G, Bach JF, et al. Benzodiazepine anesthesia in humans modulates the interleukin-1 beta, tumor necrosis factor-alpha and interleukin-6 responses of blood monocytes. J Neuroimmunol. 1991; 35(1–3):13–9. Epub 1991/12/01. doi: 10.1016/0165-5728(91)90157-3. PMID: 1955561.

30. Kim SN, Son SC, Lee SM, Kim CS, Yoo DG, Lee SK, et al. Midazolam inhibits proinflammatory mediators in the lipopolysaccharide-activated macrophage. Anesthesiology. 2006; 105(1):105–10. Epub 2006/07/01. https://doi.org/10.1097/00000542-200607000-00019 PMID: 16810001.

31. Yousefi OS, Wilhelm T, Maschke-Neuß K, Kuhny M, Martin C, Molderings GJ, et al. The 1,4-benzodiazepine Ro5-4864 (4-chlorodiazepam) suppresses multiple pro-inflammatory mast cell effector functions. Cell Commun Signal. 2013; 11(1):13. Epub 2013/02/22. https://doi.org/10.1186/1478-811X-11-13 PMID: 23425659.

32. Falcón CR, Hurst NF, Vivinetto AL, López PHH, Zurita A, Gatti G, et al. Diazepam Impairs Innate and Adaptive Immune Responses and Ameliorates Experimental Autoimmune Encephalomyelitis. Front Immunol. 2021; 12:682612. Epub 2021/08/07. https://doi.org/10.3389/fimmu.2021.682612 PMID: 34354703.

33. Joya FL, Kripke DF, Loving RT, Dawson A, Kline LE. Meta-analyses of hypnotics and infections: eszopiclone, ramelteon, zaleplon, and zolpidem. J Clin Sleep Med. 2009; 5(4):377–83. Epub 2009/12/09. PMID: 19988019.

34. Sato K, Nakashima T. Human adult deglutition during sleep. Ann Otol Rhinol Laryngol. 2006; 115 (5):334–9. Epub 2006/06/03. https://doi.org/10.1177/000348940611500503 PMID: 16739683.

35. Fass R, Quan SF, O’Connor GT, Ervin A, Iber C. Predictors of heartburn during sleep in a large prospective cohort study. Chest. 2005; 127(5):1658–66. Epub 2005/05/13. https://doi.org/10.1378/chest.127.5.1658 PMID: 15888643.

36. Yang CW, Li CI, Li TC, Liu CS, Lin CH, Lin WY, et al. Combined Effects of Having Sleep Problems and Taking Sleeping Pills on the Skeletal Muscle Mass and Performance of Community-Dwelling Elders. Sci Rep. 2019; 9(1):13760. Epub 2019/09/26. https://doi.org/10.1038/s41598-019-50295-w PMID: 31551587.