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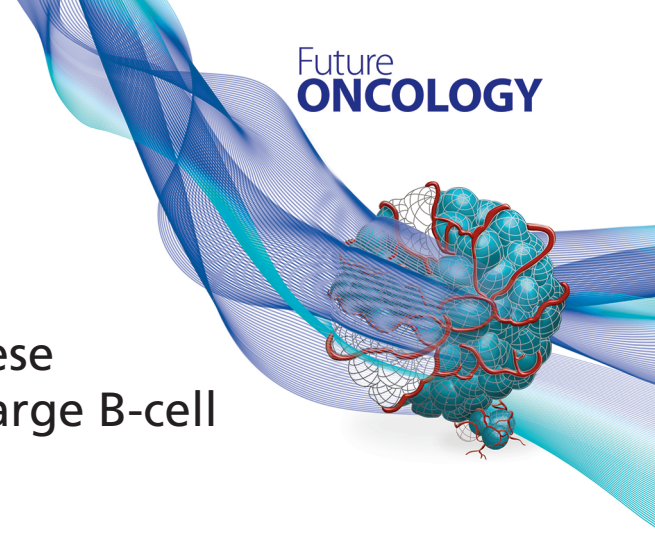

Economic burden in treated Japanese patients with relapsed/refractory large B-cell lymphoma

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Aim: To understand the economic burden of relapsed and refractory large B-cell lymphoma patients in Japan treated with salvage chemotherapy. **Patients & methods:** Patients who received systemic therapy after first-line treatment were analyzed to assess its associated cost and resource use using a retrospective claims database. The impact of COVID-19 was assessed separately. **Results & conclusion:** This study identified 2927 and 1085 patients in the second- (2L) and third-line (3L) cohorts. The median ages for the 2L and 3L cohorts were 71 and 70 years, respectively, with Charlson Comorbidity Score of 3. A majority of the patients had limited stem cell transplant due to advanced age. Median lengths of inpatient stay for the 2L and 3L cohorts were 118 and 116 days, respectively. The majority of costs were attributed to inpatient costs, and limited COVID-19 impact was observed in this study.

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Keywords: cost • COVID-19 • database study • diffuse large B-cell lymphoma • Japanese • refractory • relapse • retrospective • salvage chemotherapy

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, accounting for approximately one-third of all cases in the USA [1,2] and 35.8% of malignant lymphomas in Japan [3]. It is estimated that approximately 30–40% of patients with DLBCL will either relapse or exhibit refractory disease after chemotherapy [4]. While autologous stem cell transplant (auto-SCT) following intensive salvage chemotherapy regimens remains the standard of care (SoC) for relapsed or refractory DLBCL (r/r DLBCL), about 60% of patients with r/r DLBCL are ineligible for transplant; therefore there are high unmet medical needs for such patients, with relatively poor survival due to susceptibility of SoC or advanced age [5]. A comparison of r/r DLBCL patients with a historical population of patients treated prior to the routine use of rituximab marked relatively prolonged survival, but the prognosis of patients who experience a recurrence or progression of the disease following auto-SCT remains poor [6].

In a prior retrospective database study, approximately 70% of patients with DLBCL in Japan were found to be aged 65 years and over [7], with more than 20% aged 80 years and above [8]. As the recommended age limit for eligibility for auto-SCT is 65 years and early 70s for allogeneic stem cell transplant (allo-SCT) for those who are neither eligible for auto-SCT transplant nor failed [9], a substantial proportion of DLBCL patients require alternative therapies. Additionally, patients with r/r DLBCL who are not candidates for high-dose therapy are not considered eligible for SCT [10], and patients with double-hit lymphomas or double-expressor lymphomas have been found to have inferior progression-free survival associated with auto-SCT [11]. Such patients are therefore treated with salvage chemotherapy regimens or radiation therapy as palliative treatment [8,10]; these treatments are not for curative intent and prognosis remains poor due to both the aggressive nature of the disease and the heterogeneous clinicobiological profiles of r/r DLBCL patients [12,13]. Furthermore, uncertainties in the timing of relapse and progression found in several studies – including a significant risk of relapse of DLBCL after auto-SCT – result in a requirement for continued monitoring and a need for better prognostic tools to be established for

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better clinical decision-making [14,15]. Given that the determining factor for prognosis in relapse is still subject to debate, absolute lymphocyte count, LDH and a proxy for time to relapse (time between second- [2L] or third-line [3L] index treatment and prior treatment) were explored in this study of r/r DLBCL patients in Japan, to the extent where data were available.

To our knowledge, there is no standard treatment regimen or definite treatment consensus for patients with r/r DLBCL who are not eligible for auto-SCT or who relapse after auto-SCT [8]. Recently, chimeric antigen receptor T-cell (CAR-T) therapies have been approved to treat such a population. However, obstacles such as the limited number of institutions that are able to provide treatment with this technology and the resultant limited availability of treatment capacity still exist. Because the approval of the first CAR-T product in Japan was in 2019, we could not capture patients treated with CAR-T in this study based on the study period and inclusion/exclusion criteria of this study.

Therefore the primary objective of this study is to elucidate the existing SoC for r/r DLBCL from the perspective of treatment patterns and economic burden associated with second and third lines of therapy. As a secondary objective, we attempted to assess how the COVID-19 pandemic may have affected the SoC in Japan from 1 March to 30 June 2020, using the same months in the previous year as reference [16,17]. We evaluated the potential degree of changes in healthcare resource utilization (HCRU), costs and treatment patterns as a result of the onset of the pandemic to understand the most up-to-date real world clinical landscape for r/r DLBCL patients in Japan.

Patients & methods

Database & patient selection

In this study the Medical Data Vision (MDV) database was used to evaluate treatment patterns associated with 2L and 3L therapy for r/r DLBCL patients stratified by regimen groups and associated economic burden. The MDV database is an electronic health records-based database comprised of anonymized hospital data from 374 hospitals, covering approximately 22% of acute-phase hospitals and including data for 25.57 million people. The MDV database has an age distribution similar to that of the Japanese national population [18]. Of all acute hospitals covered by MDV, 187 are cancer therapeutic facilities, which provide sufficient data for the objectives of the study. The database includes diagnosis procedure combination claims, comprised of a dataset of inpatient and outpatient encounters, drugs prescribed, diagnoses and laboratory tests performed.

The identification period of this study was designed based on a prior Japanese study on DLBCL patients [8], from 1 October 2008 through 31 December 2018 for the main analysis cohort, from 1 March through 30 June 2019 for the pre-COVID-19 subgroup, and from 1 March through 30 June 2020 for the post-COVID-19 subgroup (Supplementary Figure 1A & B, respectively). Patients included in this study were those with a minimum look-back period of 6 months and a minimum follow-up period of 12 months relative to their index date. In both the main analysis and COVID-19 subgroups, the index date was defined as the date of initiation of 2L therapy for the 2L cohort, and 3L therapy for the 3L cohort. The study period continued until 31 December 2019 for the main analysis cohort. The pre-COVID-19 and post-COVID-19 subgroups were comprised of patients whose index date and analysis periods were 1 March–30 June 2019 and 1 March–30 June 2020, respectively. Separately, claims between 1 March and 30 June 2019 for the pre-COVID-19 subgroup were analyzed in comparison with claims between 1 March and 30 June 2020 for the post-COVID-19 subgroup (Supplementary Figure 2).

Patients included in this study were those treated for r/r DLBCL during the look-back and identification periods, and who had claims with an International Classification of Diseases (ICD-10) diagnosis code for DLBCL (C83.3x, C85.2x, Japanese *receiptcode* 8847286) on the date of their first DLBCL treatment or within 6 months prior to their first treatment date [8]. The date of their first DLBCL treatment was designated as the first treatment date, and the date of initiation of 2L or 3L DLBCL treatment was designated as the index date. Patients who did not have at least two claims (for any disorder) within the 1-year follow-up (one claim every 6 months, unless they died within the first 6 months) from the index date, or who did not have at least one claim (for any disorder) during the 6-month look-back period, were excluded from the analysis. The same inclusion and exclusion criteria were applied to the COVID-19 analysis subgroups, with the exception that patients were required to have one additional claim recorded during the 4-month analysis period after their index date (Supplementary Figure 2).

Line progression was defined as when a new drug that was not included in the initial treatment regimen was added after 30 days from the first treatment date or when the patient had a gap of more than 90 days in receiving any type of treatment (Figure 1). Patients were considered to be in the same line of therapy if they stayed on the same regimen as their initial treatment regimen without a gap; initial treatment consisted of all drugs taken ±30 days around the

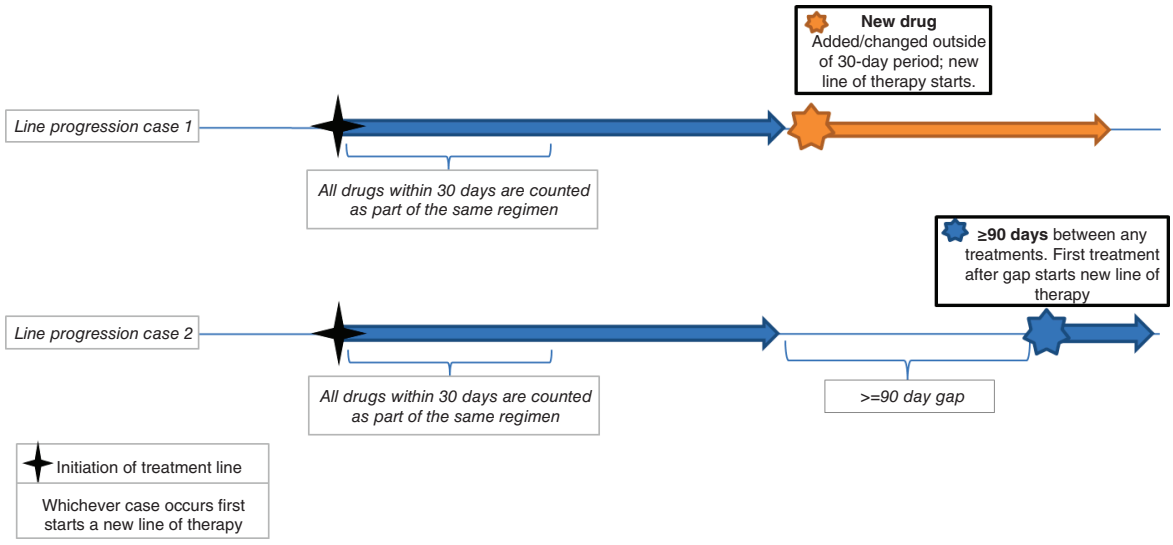

Figure 1. Definition of line progression.

first treatment date. Patients who did not progress to 2L or 3L treatments were excluded from the analysis cohorts. Additionally, only patients whose index regimen (2L, 3L) could be classified into a group as identified were included. Treatments were grouped into regimens based on their combination of systemic therapy with or without rituximab (+/− R). A hierarchy of regimens allowed patients to be classified into only one group: DeVIC (dexamethasone, etoposide, ifosfamide, carboplatin)-based with or without rituximab (+/− R); CHASE (cyclophosphamide, cytarabine, etoposide, dexamethasone)-based (+/− R); GDP (gemcitabine, dexamethasone, cisplatin)-based (+/− R); R-Bendamustine; EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)-based (+/− R); ESHAP (etoposide, cytarabine, cisplatin, methylprednisolone)-based (+/− R); R-CVP (rituximab, cyclophosphamide, vincristine, prednisolone)-based; ICE (ifosfamide, carboplatin, etoposide)-based (+/− R); DHAP (dexamethasone, cytarabine, cisplatin)-based (+/− R); or 'Other' chemotherapy (+/− R) (including other rituximab-based chemotherapy, except for R-CHOP and other chemotherapy without rituximab). R-CHOP was excluded from this analysis as it is generally not used as a treatment for r/r DLBCL in clinical practice. As only specific combinations were considered for selection into the 2L and 3L cohorts, all other treatment combinations prescribed in subsequent lines of therapy but not explicitly defined in selection of 2L and 3L or excluded from 2L and 3L cohorts were classified under 'others (not specified)'. These regimens include R-CHOP and conditioning therapies for SCT, which were excluded from index regimens, as well as ibrutinib, lenalidomide or other targeted/immunotherapy without chemotherapy.

Ethics approval & consent to participate

This study was a retrospective study utilizing an existing hospital claims database, with no primary data collection involved. Inclusion of patient records in the database was conditional upon notification to patients that their inpatient/outpatient claims data would be used for research via an opt-out system. All data in this database were deidentified prior to addition, and patient records were only linked within each unique facility. As such, with all data anonymized, the Ethical Guidelines for Epidemiological Research in Japan are not applicable to this study [19]. In addition, the Ethical Guidelines on Biomedical Research Involving Human Subjects ascertain that written informed consent from patients is not required for such pharmacoepidemiological studies conducted using medical databases, as the use of pre-existing data does not require any interaction with patients [20].

Data analysis

This study included: baseline patient characteristics for each main analysis cohort; treatment patterns, including proportion of patients on each regimen group from 1L to 6L+, duration of each regimen and proportion of patients on radiation therapy for each main analysis cohort; trends in index dosage for each 2L or 3L regimen, stratified by age; HCRU, including use of radiation therapy and SCT; direct medical costs; and the impact of COVID-19 on treatment patterns and HCRU. Costs and utilization of specific procedures, such as radiation therapy and SCT,

were calculated based on the Japanese reimbursement codes for such procedures and do not include further care or follow-up associated with the procedures. As the objectives of the study were to describe the treatment landscape and the associated burden of disease for r/r DLBCL overall, no propensity score matching was conducted. Additionally, in all outcomes, no specific regimen was directly compared against another regimen.

In dosage analysis, only patients with available baseline body surface area data were included. The dosage units for each drug under each regimen are presented as mg, mg/m^2 or mg/kg, according to the guidelines of administration. The results are stratified by <65 years and 65+ years of age based on the definition of elderly patients. A separate analysis of cost, HCRU and baseline characteristics was also conducted for patients who underwent auto-SCT with prior conditioning therapy under the following regimens: mitoxantrone, ifosfamide, mesna, etoposide (MINE), melphalan, cyclophosphamide, etoposide, dexamethasone (LEED), ranimustine, etoposide, cytarabine, melphalan (MCEC), ranimustine, carboplatin, etoposide, cyclophosphamide (MEAM) (auto-SCT cohort). HCRU measures included the number of outpatient visits, number of inpatient stays, average length of stay (LOS) and number of emergency room (ER) visits during each line of therapy. Costs were obtained as unadjusted nominal direct medical costs in Japanese yen from the database and presented as direct adjusted nominal costs in US dollars (USD; for conversion, see Supplementary Table 1), stratified by inpatient costs, outpatient costs, cancer treatment costs, other pharmacy costs, cost of radiation therapy and cost of SCT. End-of-life costs were calculated for a subgroup of patients who had a death record in the database and were summed up during the last month prior to their death. The impact of COVID-19 was analyzed for time to progression to their first line of therapy, number of deaths, number of outpatient visits, number of inpatient admissions, number of ER visits, number of intensive care unit (ICU) stays, number of radiation therapy procedures and number of SCTs.

All data analyses were performed using SAS® version 9.4 or higher (https://support.sas.com/software/94/). Continuous variables were summarized using mean, standard deviation (SD), median, minimum and maximum. Categorical variables were summarized using frequency and percentage. For HCRU and costs, analysis of variance or the univariate generalized linear model was used for continuous outcomes depending on the data distribution, and χ-square was used for categorical outcomes. The p-values for cost outcomes were calculated based on a γ-distributed log-link generalized linear model. All analyses were performed in a manner consistent with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [21] and applicable sections of the Consolidated Standards of Reporting Trials guidelines [22].

Results

Patient characteristics

During the study identification period (1 October 2008 to 31 December 2018), there were 17,246 patients with a DLBCL diagnosis on or within 6 months prior to their first treatment date. Of these, 4376 patients initiated their 2L treatment and 1946 patients initiated their 3L treatment during the identification period. After applying additional exclusion criteria, 2927 patients remained in the 2L cohort, 59 patients in the 2L auto-SCT cohort, 1085 patients in the 3L cohort and 77 patients in the 3L auto-SCT cohort. For the secondary analysis cohorts, 322 and 318 patients fulfilled the criteria for the 2L pre-COVID-19 and post-COVID-19 subgroups, respectively, and 48 and 40 patients for the 3L pre-COVID-19 and post-COVID-19 subgroups, respectively. Patient attrition is illustrated in Supplementary Figure 1A & B.

Patient characteristics (Table 1) show that the mean (SD) ages for 2L and 3L cohorts were comparable, at 69.2 (12.3) years and 68.1 (12.4) years, respectively. The median ages were 71 and 70 years, respectively. The 2L and 3L auto-SCT cohorts were approximately 10 years younger on average, with the mean (SD) ages being 58.5 (7.7) years and 56.7 (11.0) years, respectively, with a median age of 60 for both sub-cohorts. No patients above the age of 75 received auto-SCT. Only one patient aged 75 years or older received SCT during 4L therapy, and no patient aged 75 years or older received SCT in any other line assessed in this study.

Treatment patterns

Treatment patterns for 2L and 3L patients were evaluated from first to sixth line of therapy, as shown in Table 2 & Supplementary Table 2. A majority of patients in both the 2L and 3L cohorts underwent other chemotherapies (50.9 and 54.7%, respectively), of whom around 82% were aged 60 and above. R-CHOP-based 1L therapy was used in 43.3% of the 2L cohort and 46.5% of the 3L cohort.

For both 2L and 3L cohorts, a larger proportion of younger patients received CHASE-based (+/− R) and EPOCH-based (+/− R) regimens for their index treatment, while patients aged 70 and above in the 2L cohort

Table 1. Patient demographics and baseline characteristics.

	2L		3L	
	2L cohort (n = 2927)	2L auto-SCT cohort (n = 59)	3L cohort (n = 1085)	3L auto-SCT cohort (n = 77)
Age on index date (years):				
Mean (SD)	69.2 (12.3)	58.5 (7.7)	68.1 (12.4)	56.7 (11.0)
Median (Q1, Q3)	71.0 (63.0, 78.0)	60.0 (54.0, 64.0)	70.0 (62.0, 77.0)	60.0 (52.0, 64.0)
Sex, n (%):				
Male	1659 (56.7)	34 (57.6)	612 (56.4)	48 (62.3)
Female	1268 (43.3)	25 (42.4)	473 (43.6)	29 (37.7)
Body surface area† (n/n missing):	2832/95	59/0	1063/22	76/1
Mean (SD)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)
Median (Q1, Q3)	1.6 (1.4, 1.7)	1.6 (1.5, 1.8)	1.6 (1.4, 1.7)	1.6 (1.5, 1.8)
Weight on index date (kg)† (n/n missing):	2834/93	59/0	1063/22	76/1
Mean (SD)	56.8 (12.0)	59.9 (12.1)	56.8 (12.0)	59.3 (12.4)
Median (Q1, Q3)	55.8 (48.0, 63.9)	57.9 (51.6, 68.0)	55.7 (47.7, 64.0)	58.3 (49.8, 66.2)
Time between index treatment and prior treatment (days)‡:				
Mean (SD)	195.7 (356.9)	33.0 (23.7)	122.2 (261.2)	31.8 (37.5)
Median (Q1, Q3)	35.0 (4.0, 218.0)	31.0 (22.0, 44.0)	30.0 (3.0, 112.0)	28.0 (20.0, 37.0)
Follow-up time (days)§:				
Mean (SD)	864.6 (668.8)	1229.6 (709.2)	759.7 (607.5)	976.6 (700.6)
Median (Q1, Q3)	627.0 (371.0, 1179.0)	1028.0 (587.0, 1857.0)	538.0 (321.0, 1010.0)	720.0 (477.0, 1300.0)
Modified Charlson Comorbidity Index during look-back period:				
Mean (SD)	4.0 (2.2)	4.5 (2.5)	4.3 (2.3)	4.5 (2.4)
Median (Q1, Q3)	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	3.0 (2.0, 6.0)	4.0 (2.0, 5.0)
Age group, n (%):				
0–18 years	8 (0.3)	0 (0.0)	2 (0.2)	0 (0.0)
18–70 years	1333 (45.5)	58 (98.3)	531 (48.9)	74 (96.1)
70+ years	1586 (54.2)	1 (1.7)	552 (50.9)	3 (3.9)

†Using closest values on or any time prior to index date.
‡Time between last treatment administered in prior line of therapy to initiation of index line of therapy.
§Duration is from index date until death or last patient record.
2L: Second-line; 3L: Third-line; auto-SCT: Autologous stem cell transplant; Q: Quartile; SD: Standard deviation.

tended to receive R-CVP-based, GDP-based (+/− R) and DeVIC-based (+/− R) treatments on a more frequent basis, and patients aged 70 and above in the 3L cohort tended to receive DeVIC-based (+/− R), GDP-based (+/− R) and EPOCH-based (+/− R) therapies more frequently.

Dosage trends in 2L & 3L cohorts

Index dosage by regimen was analyzed for each cohort, stratified by patients aged <65 years and patients aged 65 years and above. There was a general trend across both 2L and 3L cohorts of slightly lower median dosages for most drugs including gemcitabine, carboplatin, cisplatin, cyclophosphamide, cytarabine, cytosine arabinoside, gemcitabine and ifosfamide administered to the subgroup of patients aged 65 years and above, except for R-Bendamustine and LEED in the 2L cohort (Tables 3 & Supplementary Table 4).

Healthcare resource utilization

Outpatient visits

Table 4 provides a summary of HCRU during the entire patients' follow-up period after index treatment and during each line of therapy for the 2L and 3L cohorts. There is a significant difference between regimens for the number of outpatient visits during the entire follow-up period and during 2L. For the 2L cohort, the mean (SD; median) number of outpatient visits was 36.5 (30.7; 28) during the entire follow-up and 20.5 (21.1; 14) during the index line of therapy. For the 3L cohort, the mean number of outpatient visits was 18.6 (median: 12) during the index

Table 2. Treatment patterns of relapsed and refractory diffuse large B-cell lymphoma.

	2L		3L	
	2L cohort (n = 2927), n (%)	2L auto-SCT cohort (n = 59), n (%)	3L cohort (n = 1085), n (%)	3L auto-SCT cohort (n = 77), n (%)
Index regimen				
DeVIC-based ± R	216 (7.4)		90 (8.3)	
CHASE-based ± R	313 (10.7)		73 (6.7)	
GDP-based ± R	270 (9.2)		106 (9.8)	
R-bendamustine-based	85 (2.9)		36 (3.3)	
EPOCH-based ± R	140 (4.8)		91 (8.4)	
ESHAP-based ± R	80 (2.7)		41 (3.8)	
R-CVP-based, without doxorubicin	304 (10.4)		40 (3.7)	
ICE-based ± R	26 (0.9)		14 (1.3)	
DHAP-based ± R	3 (0.1)		1 (0.1)	
Other chemotherapy	1490 (50.9)		593 (54.7)	
Prior 1L regimen				
R-CHOP-based	1267 (43.3)	12 (20.3)	505 (46.5)	54 (70.1)
R-CVP-based	448 (15.3)	0 (0.0)	157 (14.5)	2 (2.6)
R-bendamustine-based	24 (0.8)	0 (0.0)	11 (1.0)	1 (1.3)
R monotherapy	39 (1.3)	0 (0.0)	8 (0.7)	2 (2.6)
R + other chemotherapy-based	543 (18.6)	43 (72.9)	203 (18.7)	8 (10.4)
Other immunotherapy-based	2 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Chemotherapy without R	467 (16.0)	4 (6.8)	161 (14.8)	10 (13.0)
Others (not specified)	137 (4.7)	0 (0.0)	39 (3.6)	0 (0.0)
Subsequent regimen (3L, only for 2L cohort)				
N with 3L	2068	30		
DeVIC-based ± R	144 (7.0)	6 (20.0)		
CHASE-based ± R	105 (5.1)	1 (3.3)		
GDP-based ± R	181 (8.8)	1 (3.3)		
R-Bendamustine-based	51 (2.5)	1 (3.3)		
EPOCH-based ± R	109 (5.3)	0 (0.0)		
ESHAP-based ± R	54 (2.6)	0 (0.0)		
R-CVP-based, without doxorubicin	59 (2.9)	0 (0.0)		
ICE-based ± R	21 (1.0)	0 (0.0)		
DHAP-based ± R	2 (0.1)	0 (0.0)		
Other chemotherapy	839 (40.6)	6 (20.0)		
Others (not specified)	503 (24.3)	15 (50.0)		

1L: First-line; 2L: Second-line; 3L: Third-line; Auto-SCT: Autologous stem cell transplant; R: Rituximab.

line. The difference in the number of outpatient visits between all regimen groups across all lines was statistically significant ($p < 0.0001$).

Inpatient admissions

For the 3L cohort, there was a mean (SD; median) of 5.0 (3.9; 4) inpatient admissions during the entire follow-up with a LOS of 144.9 (113.9; 118) days, and 2.7 (1.9; 2) admissions with a LOS of 54.2 (44.8; 41) days during the index line of therapy.

For the 2L cohort, the number of inpatient admissions and LOS was significantly different between regimen groups ($p < 0.0001$). Patients with other chemotherapy +/− R as their second line had a lower number of inpatient admissions during the entire follow-up period and during the index line of therapy and had shorter mean (SD; median) LOS at 125.0 (105.8; 97) days and 48.0 (45.9; 34) days, respectively (Supplementary Table 5). For the 3L cohort, the number of inpatient admissions and LOS were also significantly different between treatment regimens ($p < 0.0001$). Patients who underwent other chemotherapy +/− R as their third line had a slightly lower number

Table 3. Dosage trends in 2L & 3L cohorts.

Regimen	Drug	Median dosage	Drug	Median dosage
Median index dosage per regimen, 2L cohort				
R ± GDP-based, n = 266	**Age <65 years, n = 42**		**Age 65+ years, n = 224**	
	Gemcitabine	983.0 mg/m^2	Gemcitabine	882.5 mg/m^2
	Dexamethasone	39.0 mg	Dexamethasone	33.0 mg
	Cisplatin, n = 30	73.0 mg/m^2	Cisplatin, n = 124	59.5 mg/m^2
	Carboplatin, n = 14	475.0 mg	Carboplatin, n = 102	400.0 mg
	Rituximab, n = 26	382.0 mg/m^2	Rituximab, n = 167	384.0 mg/m^2
R ± CHASE-based, n = 306	**Age <65 years, n = 175**		**Age 65+ years, n = 131**	
	Cyclophosphamide	1203.0 mg/m^2	Cyclophosphamide	1163.0 mg/m^2
	Cytosine arabinoside	1971.0 mg/m^2	Cytosine arabinoside	1523.0 mg/m^2
	Etoposide	118.7 mg/m^2	Etoposide	115.2 mg/m^2
	Dexamethasone	33.0 mg	Dexamethasone	33.0 mg
	Rituximab, n = 152	386.5 mg/m^2	Rituximab, n = 106	385.0 mg/m^2
R ± DHAP-based, n = 3	**Age <65 years, n = 1**		**Age 65+ years, n = 2**	
	Cisplatin	106.0 mg/m^2	Cisplatin	73.5 mg/m^2
	Cytosine	4224.0 mg/m^2	Cytosine	2666.5 mg/m^2
	Dexamethasone	20.0 mg	Dexamethasone	25.0 mg
	Rituximab, n = 1	411.0 mg/m^2	Rituximab, n = 1	615.0 mg/m^2
R ± DeVIC-based, n = 213	**Age <65 years, n = 42**		**Age 65+ years, n = 171**	
	Dexamethasone	33.0 mg	Dexamethasone	33.0 mg
	Etoposide	113.7 mg/m^2	Etoposide	98.8 mg/m^2
	Ifosfamide	1705.5 mg/m^2	Ifosfamide	1330.0 mg/m^2
	Carboplatin	307.0 mg/m^2	Carboplatin	239.0 mg/m^2
	Rituximab, n = 30	388.0 mg/m^2	Rituximab, n = 141	380.0 mg/m^2
R ± EPOCH-based, n = 135	**Age <65 years, n = 48**		**Age 65+ years, n = 87**	
	Etoposide	63.8 mg/m^2	Etoposide	61.9 mg/m^2
	Prednisolone	53.8 mg/m^2	Prednisolone	43.7 mg/m^2
	Vincristine	0.6 mg/m^2	Vincristine	0.6 mg/m^2
	Cyclophosphamide	770.5 mg/m^2	Cyclophosphamide	713.0 mg/m^2
	Doxorubicin	12.8 mg/m^2	Doxorubicin	11.5 mg/m^2
	Rituximab, n = 44	383.5 mg/m^2	Rituximab, n = 71	383.0 mg/m^2
R ± ESHAP-based, n = 78	**Age <65 years, n = 26**		**Age 65+ years, n = 52**	
	Etoposide	62.3 mg/m^2	Etoposide	61.8 mg/m^2
	Cytarabine	1980.5 mg/m^2	Cytarabine	1672.5 mg/m^2
	Cisplatin	26.0 mg/m^2	Cisplatinum	22.0 mg/m^2
	Methylprednisolone	500.0 mg	Methylprednisolone	500.0 mg
	Rituximab, n = 17	391.0 mg/m^2	Rituximab, n = 39	379.0 mg/m^2
R ± ICE-based, n = 26	**Age <65 years, n = 10**		**Age 65+ years, n = 16**	
	Ifosfomide	3319.0 mg/m^2	Ifosfomide	1318.0 mg/m^2
	Carboplatin	600.0 mg	Carboplatin	425.0 mg
	Etoposide	106.8 mg/m^2	Etoposide	106.8 mg/m^2
	Rituximab, n = 7	380.0 mg/m^2	Rituximab, n = 13	389.0 mg/m^2
R-CVP-based, without doxorubicin, n = 296	**Age <65 years, n = 17**		**Age 65+ years, n = 279**	
	Rituximab	355.0 mg/m^2	Rituximab	380.0 mg/m^2
	Cyclophosphamide	693.0 mg/m^2	Cyclophosphamide	594.0 mg/m^2
	Vincristine	1.2 mg/m^2	Vincristine	1.2 mg/m^2
	Prednisolone	46.0 mg	Prednisolone	33.0 mg
R-Bendamustine-based, n = 84	**Age <65 years, n = 18**		**Age 65+ years, n = 66**	
	Rituximab	371.5 mg/m^2	Rituximab	377.0 mg/m^2
	Bendamustine	105.0 mg/m^2	Bendamustine	118.0 mg/m^2

2L: Second-line; 3L: Third-line; R: Rituximab.

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Table 3. Dosage trends in 2L & 3L cohorts (cont.).

Regimen	Drug	Median dosage	Drug	Median dosage
Median index dosage per regimen, 3L cohort				
R± GDP-based, n = 106	**Age <65 years, n = 23**		**Age 65+ years, n = 83**	
	Gemcitabine	1032.0 mg/m^2	Gemcitabine	837.0 mg/m^2
	Dexamethasone	33.0 mg	Dexamethasone	33.0 mg
	Cisplatin, n = 18	74.9 mg/m^2	Cisplatin, n = 43	59.2 mg/m^2
	Carboplatin, n = 5	500.0 mg	Carboplatin, n = 40	300.0 mg
	Rituximab, n = 13	387.0 mg/m^2	Rituximab, n = 62	382.0 mg/m^2
R ± CHASE-based, n = 72	**Age <65 years, n = 35**		**Age 65+ years, n = 37**	
	Cyclophosphamide	1180.0 mg/m^2	Cyclophosphamide	952.0 mg/m^2
	Cytosine arabinoside	1925.0 mg/m^2	Cytosine arabinoside	1404.0 mg/m^2
	Etoposide	113.2 mg/m^2	Etoposide	95.4 mg/m^2
	Dexamethasone	33.0 mg	Dexamethasone	33.0 mg
	Rituximab, n = 27	392.0 mg/m^2	Rituximab, n = 30	387.0 mg/m^2
R ± DHAP-based, n = 1	**Age <65 years, n = 0**		**Age 65+ years, n = 1**	
	Cisplatin	–	Cisplatin	77.2 mg/m^2
	Cytosine	–	Cytosine	1802.0 mg/m^2
	Dexamethasone	–	Dexamethasone	33.0 mg
R ± DeVIC-based, n = 89	**Age <65 years, n = 31**		**Age 65+ years, n = 58**	
	Dexamethasone	33.0 mg	Dexamethasone	33.0 mg
	Etoposide	119.6 mg/m^2	Etoposide	111.0 mg/m^2
	Ifosfamide	1686.0 mg/m^2	Ifosfamide	1357.5 mg/m^2
	Carboplatin	302.0 mg/m^2	Carboplatin	246.0 mg/m^2
	Rituximab, n = 22	380.0 mg/m^2	Rituximab, n = 47	382.5 mg/m^2
R ± EPOCH-based, n = 91	**Age <65 years, n = 30**		**Age 65+ years, n = 61**	
	Etoposide	66.8 mg/m^2	Etoposide	67.0 mg/m^2
	Prednisolone	59.5 mg/m^2	Prednisolone	55.0 mg/m^2
	Vincristine	0.6 mg/m^2	Vincristine	0.7 mg/m^2
	Cyclophosphamide	818.5 mg/m^2	Cyclophosphamide	724.0 mg/m^2
	Doxorubicin	13.2 mg/m^2	Doxorubicin	12.4 mg/m^2
	Rituximab, n = 26	393.5 mg/m^2	Rituximab, n = 53	380.0 mg/m^2
R ± ESHAP-based, n = 41	**Age <65 years, n = 18**		**Age 65+ years, n = 23**	
	Etoposide	58.8 mg/m^2	Etoposide	58.7 mg/m^2
	Cytarabine	1997.5 mg/m^2	Cytarabine	1603.0 mg/m^2
	Cisplatinum	25.1 mg/m^2	Cisplatinum	21.5 mg/m^2
	Methylprednisolone	250.0 mg	Methylprednisolone	500.0 mg
	Rituximab, n = 12	387.5 mg/m^2	Rituximab, n = 17	389.0 mg/m^2
R ± ICE-based, n = 14	**Age <65 years, n = 5**		**Age 65+ years, n = 9**	
	Ifosfomide	5110.0 mg/m^2	Ifosfomide	1224.0 mg/m^2
	Carboplatin	750.0 mg	Carboplatin	330.0 mg
	Etoposide	113.8 mg/m^2	Etoposide	87.0 mg/m^2
	Rituximab, n = 4	388.5 mg/m^2	Rituximab, n = 9	395.0 mg/m^2
R-CVP-based, without doxorubicin, n = 40	**Age <65 years, n = 8**		**Age 65+ years, n = 32**	
	Rituximab	359.5 mg/m^2	Rituximab	385.0 mg/m^2
	Cyclophosphamide	703.5 mg/m^2	Cyclophosphamide	639.5 mg/m^2
	Vincristine	1.2 mg/m^2	Vincristine	1.2 mg/m^2
	Prednisolone	32.0 mg	Prednisolone	36.0 mg
R-bendamustine-based, n = 36	**Age <65 years, n = 3**		**Age 65+ years, n = 33**	
	Rituximab	391.0 mg/m^2	Rituximab	371.0 mg/m^2
	Bendamustine	103.0 mg/m^2	Bendamustine	75.0 mg/m^2

2L: Second-line; 3L: Third-line; R: Rituximab.

Table 4. Healthcare resource utilization during the follow-up period overall, by line of therapy.

	2L cohort (n = 2927)	3L cohort (n = 1085)
Number of outpatient visits		
During follow-up, n	2842	1053
Mean (SD)	36.5 (30.7)	34.2 (29.0)
Median (Q1, Q3)	28.0 (15.0, 49.0)	27.0 (13.0, 46.0)
During index treatment, n	2441	921
Mean (SD)	20.5 (21.1)	18.6 (20.4)
Median (Q1, Q3)	14.0 (5.0, 28.0)	12.0 (5.0, 26.0)
During 3L (only for 2L cohort), n	1635	
Mean (SD)	17.3 (20.5)	
Median (Q1, Q3)	11.0 (4.0, 23.0)	
Number of inpatient admissions		
During follow-up, n	2833	1057
Mean (SD)	5.1 (3.8)	5.0 (3.9)
Median (Q1, Q3)	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)
During index treatment, n	2757	1020
Mean (SD)	2.9 (1.9)	2.7 (1.9)
Median (Q1, Q3)	2.0 (2.0, 4.0)	2.0 (1.0, 4.0)
During 3L (only for 2L cohort), n	1884	
Mean (SD)	2.4 (1.7)	
Median (Q1, Q3)	2.0 (1.0, 3.0)	
Length of stay (among hospitalized patients), days		
During follow-up, n	2833	1057
Mean (SD)	140.0 (107.3)	144.9 (113.9)
Median (Q1, Q3)	116.0 (60.0, 192.0)	118.0 (59.0, 199.0)
During index treatment, n	2757	1020
Mean (SD)	57.7 (46.1)	54.2 (44.8)
Median (Q1, Q3)	45.0 (25.0, 80.0)	41.0 (24.0, 72.0)
During 3L (only for 2L cohort), n	1884	
Mean (SD)	49.8 (41.8)	
Median (Q1, Q3)	38.0 (22.0, 67.0)	
Number of stem cell transplants		
During follow-up, n	413	215
Mean (SD)	1.0 (0.2)	1.1 (0.3)
Median (Q1, Q3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
During index treatment, n	74	99
Mean (SD)	1.0 (0.0)	1.0 (0.2)
Median (Q1, Q3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
During 3L (only for 2L cohort), n	203	
Mean (SD)	1.0 (0.2)	
Median (Q1, Q3)	1.0 (1.0, 1.0)	

2L: Second-line; 3L: Third-line; Q: Quartile; SD: Standard deviation.

of inpatient admissions and shorter LOS during the entire follow-up period and during the index line of therapy (Supplementary Table 5).

ER & ICU

Only 127 patients (4.3%) from the 2L cohort and 55 patients (5.1%) from the 3L cohort had ER visits throughout the entire follow-up period. The proportion of patients with ICU admissions throughout the entire follow-up period was even lower, at 83 patients (2.8%) for the 2L cohort and 30 (2.8%) for the 3L cohort (Supplementary Table 5).

Radiation therapy

There were 830 patients (28.4%) from the 2L cohort and 293 (27.0%) from the 3L cohort who underwent radiation therapy during their follow-up period. The mean (SD; median) number of radiation therapy procedures carried out for the 2L cohort was significantly different between treatment regimens ($p < 0.0001$), at 22.0 (12.5; 20) during the entire follow-up period and 19.2 (9.1; 20) during the second line (Supplementary Table 5).

SCT procedure

During the entire follow-up period, 413 patients (14.1%) in the 2L cohort and 215 (19.8%) in the 3L cohort underwent SCT. In the 3L cohort, 23.1% of patients with other chemotherapy +/− R as 3L treatment underwent SCT, with the majority (70.1%) receiving SCT during their third line. Most patients in both cohorts who received SCT underwent auto-SCT, with the majority being between 50 and 69 years of age. Among all patients who received any SCTs, 2.7% (2L cohort) and 3% (3L cohort) were aged 70+ years (Supplementary Tables 5 & 6).

Medical costs

Across both 2L and 3L cohorts, the total costs were highest during the respective index line therapy, which also had the longest average duration (Table 4). Overall, across all lines, inpatient costs accounted for the majority of total cost.

Total costs

The mean (SD; median) total costs for the 2L cohort were USD77,173.5 (59,643.2; 62,848.0) during the entire follow-up and USD33,210.1 (25,559.1; 28,056.8) during the index line of therapy. The cost differences between regimens in both periods were statistically significant for the 2L cohort ($p < 0.0001$). The 3L cohort had mean (SD; median) total costs of USD79,118.0 (60,657.00; 62,576.3) during the entire follow-up period and USD31,414.6 (26,109.8; 25,761.5) during the index line of therapy (Table 5).

All inpatient costs

Inpatient costs contributed to the majority of the total costs across all cohorts. For the 2L cohort, inpatient costs among patients with any admissions were at a mean (SD; median) of USD64,547.1 (54,326.9; 50,810.4) over the entire follow-up period and USD28,354.9 (23,089.3; 22,590.6) during the index line of therapy (Table 5).

Pharmacy costs

Cancer treatment costs were found to account for approximately 20% of total costs, while other pharmacy costs accounted for around 25% of total costs across both cohorts. The average cost of allo-SCTs was nearly twice the cost of auto-SCT overall and by line of therapy (Supplementary Table 7).

End-of-life costs

The median cost of end-of-life care (1 month prior to death) was USD10,211.7 for the 2L cohort and USD10848.8 for the 3L cohort, with means (SD) of USD12,742.6 (9,116.5) and USD13,195.7 (9,282.5), respectively (Table 5).

Assessment on COVID 19 impact

Treatment patterns and HCRU were analyzed for the pre- and post-COVID-19 subgroups for both 2L and 3L patients, and the results are presented in Table 6 and Supplementary Table 8. Overall, mean (SD; median) time for progression to 1L of therapy increased for the 2L cohort from 253.9 (481.0; 40.5) to 318.7 (576.8; 44.5) days ($p = 0.1233$), while minimal difference was observed for the 3L cohort.

Discussion

Less than half of patients in both the 2L and 3L cohorts underwent one of the prespecified treatment regimens, although no regimen was notably administered during the index and subsequent regimens. Due to the relatively older patient population of our study (median ≥70 years in both 2L and 3L cohorts), who are likely ineligible for SCT, the heterogeneous salvage regimens reflect the nature of the population and the small number of SCT procedures observed in this study (14 and 20% for 2L and 3L cohorts, respectively). Another study also provided a different perspective on adopting alternative therapies to R-CHOP for elderly patients with DLBCL from

Table 5. Adjusted direct nominal medical costs during the follow-up period overall, by line of therapy.

	2L, all regimens (n = 2927)	3L, all regimens (n = 1085)
Total cost, US$		
During follow-up, n	2927	1085
Mean (SD)	77,173.5 (59,643.2)	79,118.0 (60,657.0)
Median (Q1, Q3)	62,848.0 (36,286.3, 99,202.7)	62,576.3 (36,614.1, 105,864.8)
During index treatment, n	2927	1085
Mean (SD)	33,210.1 (25,559.1)	31,414.6 (26,109.8)
Median (Q1, Q3)	28,056.8 (15,629.8, 44,143.5)	25,761.5 (14,334.8, 40,894.3)
During 3L (only for 2L cohort), n	2068	
Mean (SD)	28,020.9 (24,860.0)	
Median (Q1, Q3)	22,596.8 (12,075.8, 36,635.1)	
Inpatient costs, US$		
During follow-up, n	2833	1057
Mean (SD)	64,547.1 (54,326.9)	66,798.9 (56,591.0)
Median (Q1, Q3)	50,810.4 (25,646.3, 86,348.7)	51,174.6 (26,944.8, 89,461.3)
During index treatment, n	2757	1020
Mean (SD)	28,354.9 (23,089.3)	26,965.7 (23,239.4)
Median (Q1, Q3)	22,590.6 (11,798.3, 39,229.7)	21,550.5 (11,562.8, 34,950.9)
During 3L (only for 2L cohort), n	1884	
Mean (SD)	24,734.7 (21,526.9)	
Median (Q1, Q3)	19,642.5 (10,404.5, 32,522.0)	
Outpatient costs, US$		
During follow-up, n	2842	1053
Mean (SD)	15,139.0 (22,040.1)	14,469.8 (20,110.9)
Median (Q1, Q3)	8487.7 (3818.9, 18,215.0)	7881.5 (3321.7, 16,929.8)
During index treatment, n	2441	921
Mean (SD)	7796.6 (11,019.8)	7144.2 (11,213.9)
Median (Q1, Q3)	4151.3 (1324.2, 10,112.2)	3580.5 (1250.5, 8517.5)
During 3L (only for 2L cohort), n	1635	
Mean (SD)	6940.1 (13,076.5)	
Median (Q1, Q3)	3286.0 (1119.7, 8020.7)	
Total cost of end-of-life care (1 month prior to death), US$		
n	918	419
Mean (SD)	12,742.6 (9116.5)	13,195.7 (9282.5)
Median (Q1, Q3)	10,211.7 (7179.8, 16,225.7)	10,848.8 (7368.0, 16,449.7)

2L: Second-line; 3L: Third-line; Q: Quartile; SD: Standard deviation.

1L treatment, although it was acknowledged that there is no single standard 2L therapy for SCT-ineligible r/r DLBCL patients [27]. The trend of more elderly patients receiving GDP-based and DeVIC-based therapies as both 2L and 3L regimens, as identified in this study, may warrant further investigation to understand whether these therapies result in a superior prognosis for elderly patients, especially those who are ineligible for allo-SCT. In addition, treatment differences in age were also evident in dosage analyses, where there was a general trend of reduced absolute median dosages in patients aged 65 and above. While relative dosage intensity could not be obtained from this database, the results appear to be aligned with existing studies highlighting the reduction of dosage by 15% or more in elderly patients [24–26].

As with a previous study on 1L DLBCL patients in Japan [8], inpatient costs constituted the majority of total costs throughout all lines of therapy from 2L. Although not directly comparable, this trend is different from the findings of a real-world cost study conducted on DLBCL patients in the USA [34], where outpatient costs accounted for a larger proportion of cost components. However, future paradigm shifts may be expected in line with the shift toward encouraging comprehensive support measures for outpatient chemotherapy services in the 2020 Japanese medical fee revision [35]. Several regimens approved globally and under consideration in Japan may provide a snapshot into

Table 6. COVID-19 analysis.

	2L			3L		
	Pre-COVID-19 subgroup (n = 322)	Post-COVID-19 subgroup (n = 318)	p-value	Pre-COVID-19 subgroup (n = 48)	Post-COVID-19 subgroup (n = 40)	p-value
Time between index treatment and prior treatment, days†						
Mean (SD)	253.9 (481.0)	318.8 (576.8)	0.1233	13.7 (14.3)	13.7 (15.3)	0.9916
Median (Q1, Q3)	40.5 (3.0, 282.0)	44.5 (2.0, 331.0)		5.5 (1.0, 27.5)	9.0 (1.0, 23.0)	
Death during index treatment, n (%)	5 (1.6)	4 (1.3)	1.0000	0 (0.0)	0 (0.0)	–
Number of outpatient visits, days						
During index treatment, n (%)	106 (32.9)	101 (31.8)		13 (27.1)	7 (17.5)	
Mean (SD)	3.9 (3.3)	3.4 (2.8)	0.2045	3.0 (2.0)	2.6 (1.5)	0.6329
Median (Q1, Q3)	3.0 (1.0, 5.0)	2.0 (1.0, 5.0)		2.0 (2.0, 5.0)	2.0 (1.0, 4.0)	
on average per month during index treatment						
Mean (SD)	2.6 (2.5)	2.3 (3.2)	0.4801	3.8 (2.8)	3.6 (4.0)	0.9005
Median (Q1, Q3)	1.8 (0.8, 3.3)	1.6 (0.8, 2.9)		2.1 (1.5, 6.0)	2.2 (0.8, 5.2)	
Number of inpatient admissions						
During index treatment, n (%)	297 (92.2)	300 (94.3)		44 (91.7)	38 (95.0)	
Mean (SD)	1.8 (1.1)	1.8 (1.1)	0.4586	1.3 (0.5)	1.4 (0.6)	0.3226
Median (Q1, Q3)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)		1.0 (1.0, 1.0)	1.0 (1.0, 2.0)	
On average per month during index treatment						
Mean (SD)	3.4 (5.0)	3.7 (4.7)	0.5055	5.5 (5.8)	6.7 (8.7)	0.4759
Median (Q1, Q3)	1.6 (1.0, 3.3)	1.8 (1.3, 4.3)		4.0 (1.3, 7.5)	3.3 (1.8, 7.5)	
Average length of inpatient stay, days						
During index treatment, n (%)	297 (92.2)	300 (94.3)		44 (91.7)	38 (95.0)	
Mean (SD)	27.4 (22.7)	24.1 (20.1)	0.0609	16.8 (17.0)	15.3 (14.4)	0.6840
Median (Q1, Q3)	23.0 (7.0, 41.0)	21.0 (6.0, 36.0)		7.0 (3.0, 31.0)	9.5 (4.0, 25.0)	

†Time between last treatment administered in prior line of therapy to initiation of index line of therapy.
2L: Second-line; 3L: Third-line; Q: Quartile; SD: Standard deviation.

the future of the changing treatment landscape [36–39]. The increased availability of future regimens that can be applicable in outpatient settings may shift the treatment landscape of care more toward outpatient settings in Japan as well, to potentially reduce inpatient costs [40].

Although there were no statistically significant reductions in HCRU for the COVID-19 subgroup analysis, the smaller proportion of patients with outpatient visits and the slight reduction in mean LOS appear to be in line with recently developed practical guidelines on the management of cancer patients [41], in particular for those with hematological malignancies [42]. The inevitability of continuing with radiation therapy and ensuring that patients consistently receive the necessary treatment without reduced dosages was suggested, which was corroborated by the trends observed in the COVID-19 analysis in this study. Delay of chemotherapy was not recommended for DLBCL patients or for r/r disease in international guidelines [43–45], which was also reflected by our results. In addition, as also reflected in our results, active treatment for lymphoma generally did not change the mortality risk for lymphoma patients with COVID-19 [46,47]. Global studies of oncology and COVID-19 also suggest the use of telehealth, avoidance of non-essential visits, and minimization of exposure periods [43–45,48]. Although there is some evidence of changes in medical encounters in other chronic disease practices in Japan [49–51] and increased use of telemedicine in some centers [52], the widespread use of telemedicine and treatment changes in oncology remains limited and cannot be well observed in this claims database study.

The limitations for this study are as follows: the disease associated with each drug claim is not explicitly linked, and therefore treatment groupings were made based on prior literature and based on the existence of a DLBCL diagnosis prior to a patient's index date. Additionally, complete treatment and disease history of the study population could not be fully tracked, thus patients' lines of therapy should be interpreted with caution. Also, given the nature of the claims database, the limited patient population and limited analysis period for the COVID-19 analysis, findings on prognosis and the practical impact of COVID-19 in this population are limited.

This study has delivered various novel perspectives regarding the real-world treatment patterns of r/r DLBCL patients in Japan. The results of this study serve as an initial foundation for future research on superior therapies to meet the unmet needs of patients with r/r DLBCL, who are subjected to a limited range of effective therapies. The future introduction of novel therapies currently available in other parts of the world [40] may pave the way to better care for r/r DLBCL patients in Japan.

Conclusion

Overall, most patients (~97% in both 2L and 3L groups) who underwent auto-SCT at index were 69 years old or younger. We observed limited COVID-19 impact on the treatment of r/r DLBCL in Japan in terms of HCRU. Medical costs varied greatly by regimen, although the majority of cost burden was attributed to inpatient costs across regimens and lines. Future paradigm shifts associated with the introduction of new therapies with higher efficacy may change the r/r DLBCL treatment landscape of SoC by replacing existing salvage chemotherapy, which currently serves as a palliative option.

Summary points

- The median ages for the second- (2L) and third-line (3L) cohorts of patients with relapsed or refractory diffuse large B-cell lymphoma were 71 and 70 years, respectively.
- Most patients (~97% in both the 2L and 3L groups) who underwent autologous stem cell transplantation at index were 69 years old or younger.
- Median lengths of stay for the 2L and 3L cohorts were 118 and 116 days, and the majority of costs were attributed to inpatient costs.
- There was no notable difference in the cost of end-of-life care between the 2L and 3L cohorts.
- There were limited observed differences in healthcare resource utilization between pre- and post-COVID-19 pandemic groups.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-0400

Financial & competing interests disclosure

S Tsutsué is current employee of Bristol Myers Squibb (BMS). B Crawford and J Yi are current employees of Syneos Health Japan. S Makita has received honoraria from: Celgene/BMS, Chugai, CSL Behring, Eisai, Novartis, SymBio and Takeda, outside of this work. S Tsutsué, J Yi and B Crawford have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. All data are anonymized, so the Ethical Guidelines for Epidemiological Research in Japan are not applicable to this study. In addition, the Ethical Guidelines on Biomedical Research Involving Human Subjects ascertain that written informed consent from patients is not required for such pharmaco-epidemiological studies conducted using medical databases, as the use of pre-existing data does not require any interaction with patients.

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