Original Research

Burden of Illness and Treatment Patterns in Second-line Large B-cell Lymphoma

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ABSTRACT

Purpose: : This study examined real-world treatment patterns with curative intent, adverse events, and health care resource utilization and costs in patients with relapsed or refractory large B-cell lymphoma (LBCL) to understand the unmet medical need in the United States.

Methods: : Adult patients with ≥2 LBCL diagnoses between January 1, 2012, and March 31, 2019, were identified (index date was the date of the earliest LBCL diagnosis) from MarketScan® Commercial and Medicare Supplemental Databases. Patients had ≥1 claim for any LBCL treatment, ≥6 months of data before (baseline) and ≥12 months of data after (follow-up period) the index date, and no baseline LBCL diagnosis. Treatment patterns, adverse events, and all-cause and LBCL-related health care resource utilization and costs were examined. All patients had received first-line therapy of cyclophosphamide, doxorubicin, vincristine, and prednisone with or without rituximab; etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride with or without rituximab; or regimens with anthracycline and second-line therapy with stem cell transplant (SCT)–intended intensive therapy or platinum-based chemotherapy. Patients who received an SCT-intended second-line regimen or received an SCT regardless of second-line regimen were considered SCT eligible.

Findings: : A total of 188 patients met the criteria of eligibility for SCT. Among the 119 patients who received a second-line regimen intended for SCT, only 22.7% received an SCT. Patients eligible for SCT started first-line therapy within 1 month of their LBCL index date, and the mean duration of first-line therapy was 4.1 months. The mean gap in therapy between first- and second-line therapy was 6.6 months, and the mean duration of second-line therapy was 3.0 months. During the second-line therapy treatment window (mean duration with SCT, 12.4 months; mean duration without SCT, 4.8 months), the most common regimens for patients eligible for SCT were ifosfamide, carboplatin, and etoposide with or without rituximab and gemcitabine and oxaliplatin with or without rituximab; the top 4 most common treatment-related adverse events were febrile neutropenia (56.4%), anemia (49.5%), thrombocytopenia (42.6%), and nausea and vomiting (36.2%), which were similar regardless of receipt of SCT; mean (SD) per-patient-per-month all-cause costs were $46,174 ($49,057) for patients with SCT and $45,780 ($52,813) for patients without SCT.

Implications: : Treatment patterns among patients with relapsed or refractory LBCL eligible for SCT were highly varied. Only 22.7% of patients who received an SCT-preparative regimen ultimately received SCT, which highlights the magnitude of unmet needs in this population. The occurrence of treatment-related adverse events was similar regardless of SCT status. Per-patient-per-month all-cause costs were also similar with upfront SCT costs averaged during a longer follow-up. (*Clin Ther.* 2022;44:521–536.)

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Key words: health care resource utilization and costs, large B-cell lymphoma, stem cell transplant, treatment pattern, treatment-related adverse events.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), representing approximately 25% to 30% of NHL cases.[1,2] DLBCL has an annual incidence of 5.6 per 100,000 people.[2] DLBCL is an aggressive and fast-growing cancer, with a median survival of <1 year when untreated.[3] Survival improves with treatment, and the overall age-adjusted 5-year relative survival rate from the diagnosis is 64%.[2,4,5] Although patients who respond well to therapy and remain free of events for 2 years after diagnosis have a subsequent life expectancy equivalent to their age- and sex-matched peers,[6] 2-year survival is only 20% among those who are refractory to their first-line therapy.[7]

DLBCL is the most common subtype of a broader category of large B-cell lymphomas (LBCLs),[1] which have similar treatment patterns and aggressive phenotypes.[8] In most cases, the most appropriate first-line therapy for LBCL across all disease stages is rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[8] One exception is among patients with mutations in both *c-MYC* and *BCL2* (or *BCL6*), who respond better to a more intensive up-front regimen, such as etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride (EPOCH) with rituximab.[9] In addition, other first-line regimens may be appropriate for frail patients or those with poor left ventricular function.

In the clinical trial setting, R-CHOP as first-line therapy is curative in approximately 60% of patients; however, approximately 30% of patients relapse after treatment, and approximately 10% have refractory disease.[10] For patients in whom first-line therapy fails, an autologous or allogeneic stem cell transplant (SCT) is commonly regarded as the only curative option.[11,12] However, for many patients, chemosensitivity may present a barrier to SCT, with low event-free and overall survival for those not responding to SCT-intended chemotherapy.[13,14] Although the National Comprehensive Cancer Network (NCCN) provides a list of recommended second-line regimens for patients who are candidates for SCT,[8] data are limited on the real-world treatment patterns among patients with LBCL intended to undergo SCT.

Prior real-world studies of the treatment of relapsed or refractory LBCL are focused on DLBCL and out-of-date,[15] focused on a limited population (eg, Medicare patients or veterans),[16–18] or confounded by inclusion of data from patients cured by first-line therapy.[19–21] In addition, data are limited on real-world treatment-related adverse events during second-line therapy that occur outside hospitalization for SCT.[22,23] Therefore, this study examined real-world treatment patterns with curative intent in patients with relapsed or refractory LBCL to understand where there may be opportunities to improve care (unmet medical need) for these patients in the United States. We examined real-world chemotherapy patterns among patients intended for SCT and the prevalence of treatment-related adverse events between the start of second-line therapy and third-line therapy. We also report all-cause and LBCL-related health care resource utilization and costs during this period, along with the cost of SCT. Outcomes were stratified by receipt of SCT between the start of second-line therapy and third-line therapy and by the type of SCT.

METHODS

Data Sources

This study used data from July 1, 2011, through March 31, 2019, from the IBM MarketScan Commercial Database and the IBM MarketScan Medicare Supplemental Database. The IBM MarketScan Commercial Database contains the inpatient and outpatient services and prescription drug experience of employees and their dependents covered under a variety of fee-for-service and managed care health plans. The IBM MarketScan Medicare Supplemental Database contains the health care experience (medical and pharmacy) of retirees with Medicare supplemental insurance paid for by employers. Both the Medicare-covered portion of payment (represented as coordination of benefits amount) and the employer-paid portion are included in this database. All study data were obtained using *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and *International Classification of Diseases, Tenth Revision, Clinical Modification* (ICD-10-CM) codes, *Current Procedural Terminology, Fourth Edition* codes, diagnosis related

group codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs).

All database records are statistically deidentified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Because this study used only deidentified patient records and did not involve the collection, use, or transmittal of individually identifiable data, this study was exempted from institutional review board approval.

Patient Selection

We identified adults (≥18 years of age) with at least 2 inpatient or outpatient claims on different days between January 1, 2012, and March 31, 2019, with an ICD-9-CM (200.70–200.78) or ICD-10-CM (C83.30–C83.39, C83.8, C83.9, C85.1, C85.9) diagnosis code for LBCL in any position on the claim. Claims for diagnostic procedures were not used in this initial eligibility screen. We defined the index date as the date of the first claim for LBCL in this period.

To be eligible for study inclusion, we required that patients had at least 1 pharmacy or medical claim for any LBCL antitumor treatment recommended by the NCCN guidelines or any anthracycline on or following the index date.[8] We also required that patients be continuously enrolled in a health plan within MarketScan with medical and pharmacy benefits for at least 6 months before (baseline period) and at least 12 months after the index date. Patients with <12 months of follow-up but with a record of an inpatient death during the follow-up window were retained in the study cohort. To identify patients with newly diagnosed conditions, we excluded patients with a diagnosis of LBCL on any inpatient or outpatient medical claim during the 6-month baseline period. All patients were followed up until the earliest of inpatient death, end of continuous enrollment, or end of the study period (March 31, 2019).

Line of Therapy

We constructed up to 3 lines for therapy for each included patient with LBCL, starting from the index date and using the available follow-up data for each patient. Lines of therapy were constructed by building daily drug arrays for each agent to identify continuous treatment periods. For prescriptions billed by NDC codes, we determined the medication on hand on each day based on the days' supply value recorded on the outpatient prescription claims. For injectables and infusions administered in the physician's office and billed by the HCPCS, we defined the days' supply according to the expected duration of clinical benefit indicated in package inserts. When 2 prescriptions billed by the same NDC overlapped, we assumed the patient started the new prescription after exhausting their prior prescription. When there was a new injection (billed by the HCPCS) administered before exhausting the length of the clinical benefit of prior injection of the same agent, we truncated the duration of the clinical benefit of the prior injection and initiated the period of clinical benefit for the new administration on the date of administration.

The medications used to construct lines of therapy, per the NCCN Clinical Practice Guidelines for Large B-Cell Lymphoma,[8] are presented in Supplemental Table I. Lines of therapy were defined according to the following decisions. For first-line therapy, we defined the start date as the date of the earliest prescription or administration for LBCL treatment on or after the LBCL diagnosis index date. For second- and third-line therapy, we defined the start date as the date of the earliest prescription on or after the end of the prior line of therapy. New drugs added within 30 days of the line of therapy start date were considered part of the line of therapy, but new drugs added 30 days after the line of therapy start date would indicate the beginning of a new line of therapy.

Each line of therapy continued until the earliest of the following: treatment switch, treatment discontinuation, or end of the variable follow-up period. We defined a treatment switch as any claim for a new LBCL medication at least 30 days after the line of therapy start date. The end date for the prior line of therapy was defined as the earlier of the last days' supply of the prior line of therapy or the day before the start date of the new line of therapy. We defined discontinuation of line of therapy as a gap of at least 60 days after the end of all treatments in the line of therapy. The removal of 1 drug did not constitute the end of a line of therapy. The end date was defined by the last days' supply before the gap.

On the basis of clinical practice, we applied several special considerations when constructing the lines of therapy. First, corticosteroids were included in a line of

therapy if used with other LBCL medications, but their addition or discontinued use was not used to define the start or end of a line of therapy. Second, rituximab monotherapy was considered adjunctive therapy to a primary chemotherapy line of therapy if it appeared ≤180 days after a line of therapy end date, and the line of therapy duration would be extended until a new end date event. Third, if cyclophosphamide was added >30 days after the second-line therapy start date or after a 60-day gap, it was considered an extension of second-line therapy rather than the start of third-line therapy.

Patient Cohorts

Only patients who received R-CHOP, EPOCH (with or without rituximab), or regimens with anthracycline as their first-line therapy were retained in the final study cohort. We segmented patients who received a qualifying first-line regimen into 2 groups: SCT eligible and SCT non-eligible. Patients were considered SCT eligible if they received 1 of the following SCT-intended second-line regimens: dexamethasone, cisplatin, and cytarabine with or without rituximab (DHAP); dexamethasone, cytarabine, and oxaliplatin with or without rituximab (DHAX); etoposide, methylprednisolone, cytarabine, and cisplatin with or without rituximab (ESHAP); gemcitabine, dexamethasone, and cisplatin or carboplatin with or without rituximab (GDP); gemcitabine and oxaliplatin with or without rituximab (GemOx); ifosfamide, carboplatin, and etoposide with or without rituximab (ICE); mesna, ifosfamide, and mitoxantrone with or without rituximab (MINE); or any regimen that contained a platinum-based agent (carboplatin, cisplatin, or oxaliplatin). We also considered patients to be SCT eligible if they received SCT between the start of second-line therapy and the earlier of the day before the start of third-line therapy or the end of follow-up, despite not receiving an SCT-intended second-line regimen.

We defined the second-line treatment window as the time between the start of second-line therapy and the earlier of the day before the start of third-line therapy or the end of follow-up. We segmented SCT eligible patients into those who did or did not receive SCT during the second-line treatment window. Patients who received SCT during this window were further segmented by the type of SCT: allogeneic or autologous.

Baseline Patient Characteristics

We recorded patient age and sex on the index date. We also recorded the duration of follow-up and the reason for the end of follow-up. Using claims from the 6-month baseline period, we calculated the Deyo-Charlson Comorbidity Index adapted by the National Cancer Institute,[24,25] and we captured the percentage of patients with a diagnosis code for any components of the Hematopoietic Cell Transplantation–Specific Comorbidity Index available in claims data,[26] malignancy, metastatic solid tumor, and any of the conditions included in the Deyo-Charlson Comorbidity Index that are not included in the Hematopoietic Cell Transplantation–Specific Comorbidity Index.

Treatment Patterns

For first- and second-line therapy, we captured the number and percentage of SCT eligible patients who received each regimen. For each line of therapy, we captured the duration of the therapy and the time between 2 consecutive therapies. All time measurements are reported as months, which are defined as 30 days in length. We also captured the number of patients who received chimeric antigen receptor T-cell therapy any time between the start of second-line therapy and the end of follow-up.

Treatment-Related Adverse Events

We captured the number and percentage of patients with a potential treatment-related adverse event during the second-line treatment window. Using the package inserts of drugs included in regimen construction, we developed the following list of treatment-related adverse events: acute heart failure, acute respiratory failure, anemia, febrile neutropenia, infections, leukopenia, nausea or vomiting, pneumonia, renal failure, and thrombocytopenia. The adverse events evaluated also reflect the common adverse events in the Ofatumumab Versus Rituximab Salvage Chemoimmunotherapy Followed by Autologous Stem Cell Transplant in Relapsed or Refractory Diffuse Large B Cell Lymphoma (ORCHARRD) study[27] and the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL),[28] which were landmark studies of intent-to-transplant populations.

Health Care Resource Utilization and Costs

All-cause, LBCL-related, and SCT-related health care utilization and costs were reported during the

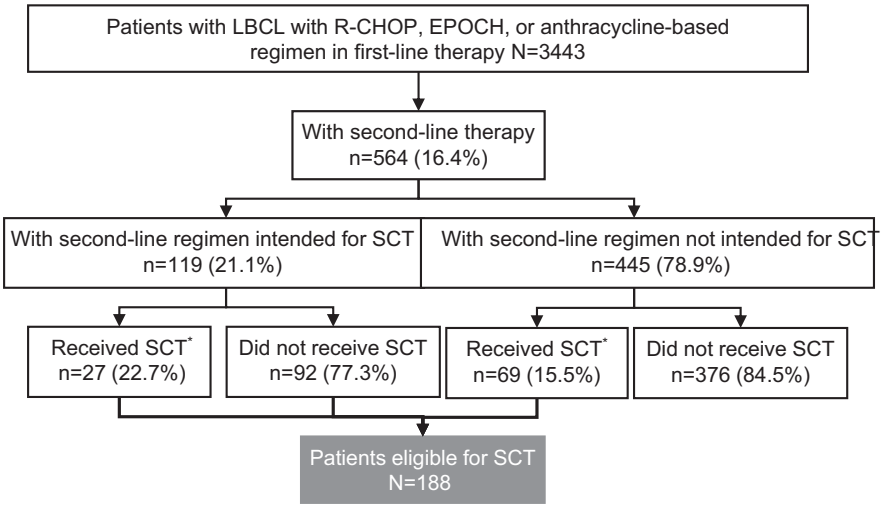


Figure 1. Stem cell transplant (SCT)–eligible cohort selection. EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride; LBCL = large B-cell lymphoma; R-CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab; SCT = stem cell transplant. *Received SCT between the start of second-line therapy and the earlier of the day before the start of third-line therapy or the end of follow-up.

second-line treatment window. LBCL-related claims were identified by medical claims with a diagnosis for LBCL (primary diagnosis during hospitalization or diagnosis in any position on outpatient medical claims), procedure or revenue claims of SCT, or outpatient pharmacy claims for LBCL medications. All-cause and LBCL-related health care resource utilization and costs were reported overall and by the following categories: inpatient admissions, outpatient care (emergency department, outpatient physician office visits, and other outpatient services), and outpatient pharmacy. LBCL-related pharmacy claims include both outpatient pharmacy claims (NDC) as well as office-administered medication claims (HCPCS) for chemotherapy, mesna, rituximab, and corticosteroids. SCT-related costs were captured by summing all costs for claims with *Current Procedural Terminology, Fourth Edition*, diagnosis related group, ICD-9-CM, or ICD-10-CM procedure codes for SCT.

Health care resource utilization and costs were calculated on a per-patient-per-month (PPPM) basis to account for the variable-length of follow-up. Costs reflect the paid amounts of fully adjudicated claims, including insurer and health plan payments, as well as patient cost-sharing in the form of copayments, deductibles, and coinsurance. Costs were inflated to 2019 US dollars using the medical care component of the Consumer Price Index.[29]

Statistical Analysis

For categorical variables, we reported the number and percentage of patients in each category and performed comparisons using χ^2 tests. For continuous variables, we reported the mean and standard deviation (SD) and performed comparisons using t tests. Statistical comparisons were made between patients who received SCT and those who did not receive SCT and between patients who received autologous SCT and those who received allogeneic SCT. A 2-sided $P < 0.05$ was specified a priori as the threshold for statistical significance.

RESULTS

Patient Selection and Characteristics

Of the 35,555 individuals with a qualifying diagnosis of LBCL between January 1, 2012, and March 31, 2019, a total of 3443 adults met all inclusion criteria and had an eligible first-line regimen (Table I). Among patients with an eligible first-line regimen, 564 received a second-line treatment, and 188 met the criteria of eligibility for SCT (Figure 1).

Table I. Patient attrition.

Attrition	No. (%) of Patients
Patients in the MarketScan Databases with at least 2 claims on different days with a diagnosis code for LBCL in any position between January 1, 2012. and March 31, 2019. The date of earliest LBCL diagnosis was set as the index date	35,555 (100)
AND at least 18 years of age on the index date	35,188 (99.0)
AND at least 1 pharmacy or medical claim for any LBCL antitumor treatment* on or following the index date	12,589 (35.4)
AND at least 6 months of continuous enrollment with medical and pharmacy benefits before the index date (baseline period)	10,795 (30.4)
AND at least 12 months of continuous enrollment with medical and pharmacy benefits after the index date or record of an inpatient death within 12 months	7098 (20.0)
AND no medical claims with a diagnosis code for LBCL diagnosis during the baseline period	6821 (19.2)
AND with R-CHOP, EPOCH (with or without rituximab), or a regimen with anthracycline† (with or without rituximab) as their first-line of DLBCL antitumor therapy	3443 (9.7)

DLBCL = diffuse large B-cell lymphoma; EPOCH = etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride; LBCL = large B-cell lymphoma; R-CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab.
*LBCL antitumor treatment recommended by the National Comprehensive Cancer Network guidelines includes the following: rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin, cytarabine, gemcitabine, oxaliplatin, ifosfamide, carboplatin, mitoxantrone, bendamustine, brentuximab vedotin, vinorelbine, lenalidomide, and procarbazine.
†Daunorubicin, epirubicin, and idarubicin.

In total, 96 patients (17.0% of those with a second-line regimen) received an SCT during the second-line treatment window. Nearly all (93.8%) these patients were commercially insured, and the mean age of patients who received SCT was 54 years. This group included 27 of the 119 patients (22.7%) who received a second-line regimen intended for SCT.

Baseline patient characteristics are reported in Table II. SCT eligible patients had a mean age of 56.7 years, and 60.6% were male. SCT non-eligible patients were a mean of 3.7 years older than SCT eligible patients ($P = 0.002$), and patients who received SCT were younger than those who did not receive SCT (54.0 vs 59.4 years, $P = 0.001$). The mean duration of follow-up was 2.4 years among all SCT eligible patients but was significantly longer for the cohort who received an SCT compared with those who did not receive an SCT (2.6 vs 2.1 years, $P = 0.006$). Inpatient death was the most common reason for the end of follow-up among all cohorts.

Characteristics of Lines of Therapy

Patients eligible for SCT started first-line therapy within a mean of 1 month of their LBCL index date, and the mean duration of first-line therapy was 4.1 months (Figure 2). The most common regimen in first-line therapy was R-CHOP (84.7%), whereas 7.4% of patients received EPOCH (with or without rituximab), and the remaining 8.0% received an anthracycline-containing regimen. The mean gap between the end of first-line therapy and the beginning of second-line therapy was 6.6 months, and the mean duration of second-line therapy was 3.0 months. In second-line therapy, the most common NCCN-recommended regimens for patients eligible for SCT were ICE (32.4%) and GemOx (19.7%) (Figure 3).

The duration of therapy and time between lines of therapy decreased as SCT eligible patients progressed to later lines of therapy (Figure 2). Of the 188 SCT eligible patients, 63 (33.5%) had evidence of a third-line chemotherapy regimen. Significantly more patients who did not receive SCT had evidence of a third-

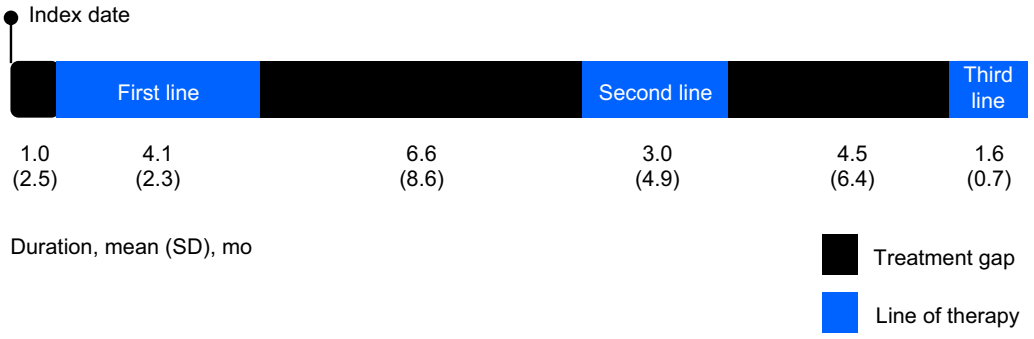


Figure 2. Line of therapy timing patterns among patients eligible for stem cell therapy. Only 63 of the 188 patients eligible for stem cell therapy had evidence of third-line therapy.

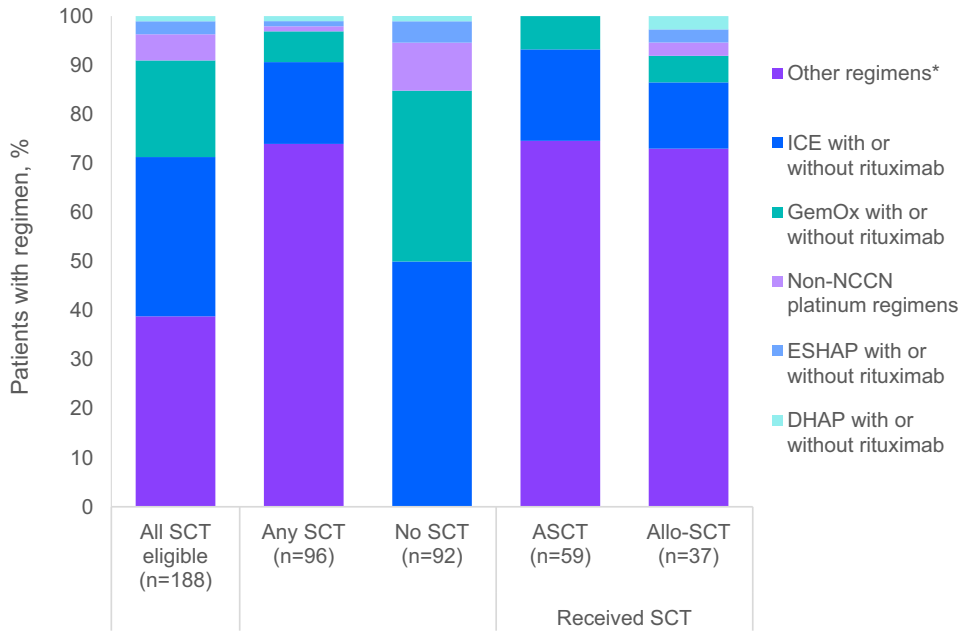


Figure 3. Treatment regimens during the second line of therapy. Allo-SCT = allogeneic SCT; ASCT = autologous SCT; DHAP = dexamethasone, cisplatin, and cytarabine with or without rituximab; ESHAP = etoposide, methylprednisolone, cytarabine, and cisplatin with or without rituximab; GemOx = gemcitabine and oxaliplatin with or without rituximab; ICE = ifosfamide, carboplatin, and etoposide with or without rituximab; NCCN = National Comprehensive Cancer Network; SCT = stem cell transplant.

*Other regimens include monotherapy of the agents, such as rituximab, as well as combinations of agents not recommended by the NCCN guidelines, including bendamustine and rituximab. In addition, R-CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone with rituximab) and EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin hydrochloride) were observed as second-line therapy for some patients.

Table II. Baseline patient characteristics

Characteristic	All Patients (N = 3443)	Second-line Therapy Patients (n = 564)			SCT Eligible Patients (n = 188)		
		SCT Eligible (n = 188)	SCT Non-eligible (n = 376)	*P*	Received Any SCT (n = 96)	Did Not Receive Any SCT (n = 92)	*P*
Age, mean (SD), y	59.2 (14)	56.7 (11.2)	60.4 (14.1)	0.002	54.0 (10.3)	59.4 (11.4)	0.001
Male, No. (%)	1960 (56.9)	114 (60.6)	224 (59.6)	0.808	57 (59.4)	57 (62.0)	0.717
NCI DCI score, mean (SD)	0.83 (1.28)	0.7 (1.2)	0.9 (1.3)	0.066	0.7 (1.1)	0.8 (1.3)	0.674
Selected baseline comorbidities,* No. (%)							
Malignancy†	2179 (63.3)	127 (67.6)	249 (66.2)	0.752	68 (70.8)	59 (64.1)	0.326
Diabetes	801 (23.3)	41 (21.8)	87 (23.1)	0.722	22 (22.9)	19 (20.7)	0.707
Psychiatric disturbance‡	478 (13.9)	19 (10.1)	50 (13.3)	0.276	10 (10.4)	9 (9.8)	0.885
COPD	455 (13.2)	16 (8.5)	58 (15.4)	0.022	7 (7.3)	9 (9.8)	0.541
Length of follow-up, mean (SD), y	2.51 (1.42)	2.35 (1.32)	2.44 (1.41)	0.467	2.61 (1.38)	2.08 (1.19)	0.006
Reason for end of follow-up, No. (%)							
Inpatient death	1823 (52.9)	107 (56.9)	219 (58.2)	0.948	53 (55.2)	54 (58.7)	0.025
End of continuous enrollment	1422 (41.3)	62 (33.0)	119 (31.6)		38 (39.6)	24 (26.1)	
End of study period	198 (5.8)	19 (10.1)	38 (10.1)		5 (5.2)	14 (15.2)	

COPD = chronic obstructive pulmonary disease; NCI DCI = National Cancer Institute–adapted Deyo-Charlson Comorbidity Index; SCT = stem cell transplant.
*Other evaluated comorbidities occurred at a frequency of <10%.
†Includes lymphoma and leukemia.
‡Includes anxiety and depression.

line therapy compared with patients who received SCT (45.7% vs 21.9%, $P < 0.001$). In addition, although the mean time from the start of second-line therapy to the start of third-line therapy was 7.3 months among all patients with a third-line therapy, this gap was 7.6 months shorter for patients who did not receive SCT compared with those who received SCT (4.8 vs 12.4 months, $P < 0.001$). A total of 14 patients received an administration of chimeric antigen receptor T-cell therapy after the start of second-line therapy, 7 of whom had received SCT in second-line therapy and 7 who had not (Supplemental Table II).

SCT

Among the 96 patients who received SCT during the second-line treatment window, 59 (61.5%) received autologous SCT, and 37 (38.5%) received allogeneic SCT. ICE and GemOx remained the most common NCCN-recommended regimens for autologous and allogeneic SCT recipients (Figure 3). The mean time between the start of second-line therapy and SCT was 3.6 months for an autologous SCT and 3.0 months for an allogeneic SCT. The percentage of patients with a third-line chemotherapy regimen was not significantly different between autologous

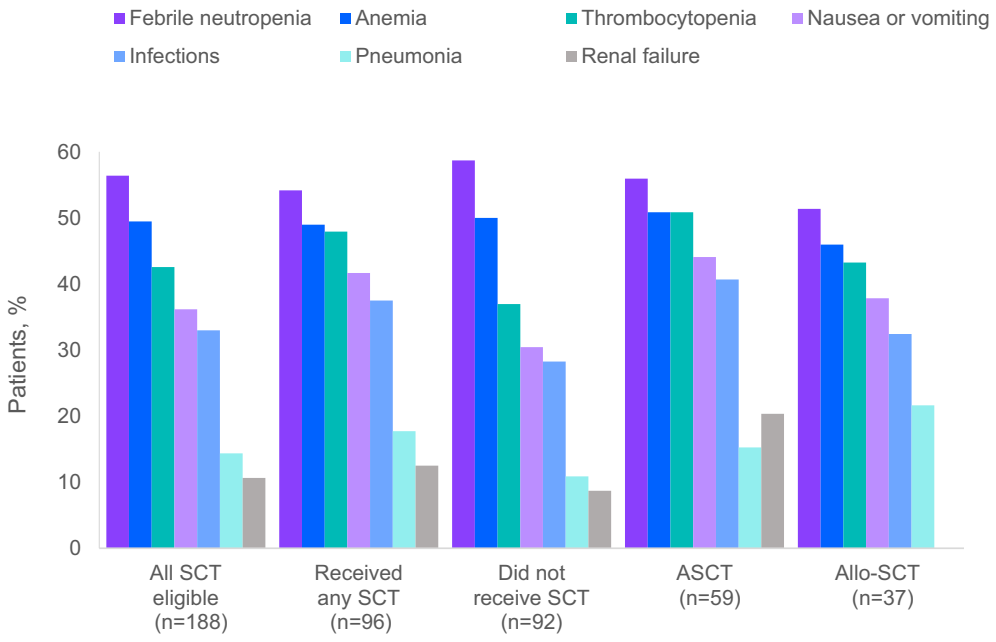


Figure 4. Percentage of patients eligible for stem cell transplant (SCT) who experienced a treatment-related adverse event. Acute heart failure, acute respiratory failure, and leukopenia occurred in <10% of all SCT-eligible patients. Allo-SCT = allogeneic SCT; ASCT = autologous SCT.

and allogeneic SCT recipients (23.7% vs 18.9%, $P = 0.579$), and the mean time from the start of second-line therapy to the start of third-line therapy was also not significantly different (11.6 vs 14.0 months, $P = 0.414$).

Treatment-Related Adverse Events

Among the 188 SCT eligible patients, the top 4 most common treatment-related adverse events during the second-line treatment window were febrile neutropenia (56.4%), anemia (49.5%), thrombocytopenia (42.6%), and nausea or vomiting (36.2%) (Figure 4). The trends were similar across all cohorts. In most cases, when comparing between patients who received SCT and those who did not receive SCT and between patients who received autologous SCT and those who received allogeneic SCT, no statistical difference was found in the percentage of patients who experienced a treatment-related adverse event. The one exception was that renal failure was more common among patients who received autologous SCT than among those who received allogeneic SCT (20.3% vs 0.0%, $P = 0.003$).

Health Care Resource Utilization and Costs

All-cause and LBCL-related health care utilization during the second-line treatment window is reported in Table III. During the second-line treatment window, 79.8% of all SCT-eligible patients had at least 1 all-cause inpatient admission, and 55.9% had at least 1 LBCL-related inpatient admission. In addition, 41.5% of all SCT eligible patients had at least 1 all-cause emergency department (ED) visit, and 6.9% had at least 1 LBCL-related ED visit.

Compared with those who did not receive SCT, significantly more patients with any SCT had an all-cause inpatient admission (99.0% vs 59.8%, $P < 0.001$) or a LBCL-related inpatient admission (95.8% vs 14.1%, $P < 0.001$) (Table III), likely because of the SCT procedure itself. By contrast, patients who received SCT had fewer all-cause or LBCL-related outpatient office visits or other outpatient services compared with patients who did not receive SCT. Possibly because of the small sample sizes, differences in health care resource utilization between patients receiving allogeneic SCT and patients receiving autologous SCT were not statistically significant.

Table III. All cause and Large B-Cell Lymphoma (LBCL)-related Healthcare Utilization During the Second-Line Treatment Window

Variable	All SCT Eligible Patients (n = 188)	SCT Eligible Patients (n = 188)			Received Any SCT (n = 96)		
		Received Any SCT (n = 96)	Did Not Receive Any SCT (n = 92)	*P*	ASCT (n = 59)	Allo-SCT (n = 37)	*P*
All-cause health care utilization							
Inpatient admissions							
Patients with an admission, No. (%)	150 (79.8)	95 (99.0)	55 (59.8)	<.001	58 (98.3)	37 (100)	>0.99
No. of inpatient admissions PPPM, mean (SD)	0.3 (0.3)	0.3 (0.3)	0.3 (0.4)	0.742	0.3 (0.3)	0.3 (0.3)	0.815
Outpatient services							
ED visits							
Patients with an ED visit, No. (%)	78 (41.5)	43 (44.8)	35 (38.0)	0.348	25 (42.4)	18 (48.6)	0.547
No. of ED visits PPPM, mean (SD)	0.6 (3.2)	0.2 (0.5)	1.1 (4.5)	0.07	0.2 (0.3)	0.3 (0.6)	0.117
Outpatient office visit							
Patients with outpatient office visit, No. (%)	187 (99.5)	96 (100)	91 (98.9)	0.489	59 (100)	37 (100)	>0.99
No. of outpatient office visits PPPM, mean (SD)	2.9 (2.1)	2.6 (1.7)	3.2 (2.4)	0.029	2.6 (1.6)	2.4 (1.8)	0.578
Other outpatient services							
Patients with other outpatient services, No. (%)	188 (100)	96 (100)	92 (100)	>0.99	59 (100)	37 (100)	>0.99
No. of other outpatient services PPPM, mean (SD)	42.9 (31.7)	34 (22.2)	52.1 (37.3)	<0.001	34.6 (23.5)	33.1 (20.2)	0.744
Outpatient pharmacy prescriptions							
Patients with an outpatient pharmacy prescription, No. (%)	185 (98.4)	96 (100)	89 (96.7)	0.115	59 (100)	37 (100)	>0.99
No. of outpatient pharmacy prescriptions PPPM, mean (SD)	4.1 (2.5)	4 (2)	4.1 (2.9)	0.925	4 (2)	4 (2)	0.99
LBCL-related health care utilization							
Inpatient admissions*							
Patients with an admission, No. (%)	105 (55.9)	92 (95.8)	13 (14.1)	<0.001	55 (93.2)	37 (100)	0.157
No. of inpatient admissions PPPM, mean (SD)	0.1 (0.1)	0.1 (0.1)	0 (0.1)	<0.001	0.1 (0.1)	0.1 (0.1)	0.64
Outpatient services							
ED visits							
Patients with an ED visit, No. (%)	13 (6.9)	4 (4.2)	9 (9.8)	0.129	1 (1.7)	3 (8.1)	0.295
No. of ED visits PPPM, mean (SD)	0.1 (0.9)	0 (0.2)	0.2 (1.3)	0.14	0 (0)	0.1 (0.3)	0.048
Outpatient office visit							
Patients with OP office visit, No. (%)	157 (83.5)	79 (82.3)	78 (84.8)	0.645	48 (81.4)	31 (83.8)	0.762

(*continued on next page*)

Table III. (*continued*)

Variable	All SCT Eligible Patients (n = 188)	SCT Eligible Patients (n = 188)			Received Any SCT (n = 96)		
		Received Any SCT (n = 96)	Did Not Receive Any SCT (n = 92)	*P*	ASCT (n = 59)	Allo-SCT (n = 37)	*P*
No. of outpatient office visits PPPM, mean (SD)	1.5 (1.8)	1.1 (1.2)	1.9 (2.2)	0.003	1.1 (1.4)	1 (0.8)	0.466
Other outpatient services							
Patients with other outpatient services, No. (%)	169 (89.9)	88 (91.7)	81 (88)	0.410	54 (92)	34 (92)	>0.99
No. of other outpatient services PPPM, mean (SD)	20.3 (25.2)	13.6 (17.0)	27.2 (30.1)	<0.001	14.4 (19.4)	12.3 (12.5)	0.556
Outpatient pharmacy claims[†]							
Patients with an outpatient pharmacy claim, No. (%)	188 (100.0)	96 (100.0)	92 (100.0)	>0.99	59 (100.0)	37 (100.0)	>0.99
No. of outpatient pharmacy claims PPPM, mean (SD)	3.4 (4.3)	1.3 (1.2)	5.6 (5.1)	<0.001	1.2 (1.0)	1.4 (1.5)	0.407

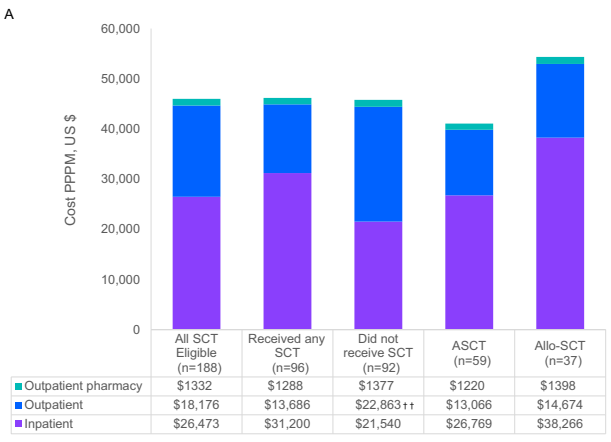
Allo-SCT = allogeneic SCT; ASCT = autologous SCT; ED = emergency department; LBCL = large B-cell lymphoma; PPPM: per patient per month; SCT = stem cell transplant; SD=standard deviation.
[*]LBCL-related admissions defined as primary diagnosis of LBCL or SCT procedure.
[†]LBCL-related pharmacy claims include both outpatient pharmacy claims (National Drug Code) as well as office-administered medication claims (Healthcare Common Procedure Coding System) for chemotherapy, mesna, rituximab, and corticosteroids.

Mean (SD) total all-cause costs during the second-line treatment window were $497,535 ($382,343) for patients who received SCT and $255,719 ($310,562) for patients who did not receive SCT ($P < 0.001$). This difference in total cost was largely driven by the cost of an SCT. Among all patients with an SCT, mean (SD) SCT costs during the second-line treatment window were $199,608 ($157,156). SCT costs were $187,235 ($116,706) for patients who received an autologous SCT and $219,338 ($206,352) for patients who received an allogeneic SCT ($P = 0.33$).

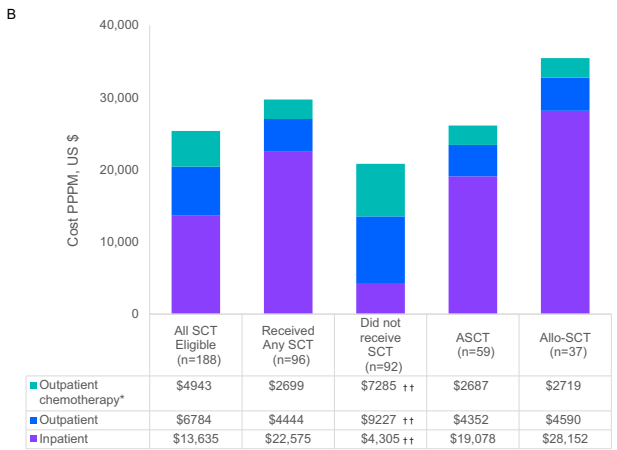
For SCT eligible patients, mean (SD) PPPM all-cause costs during the second-line treatment window were $45,981 ($50,793), and LBCL-related costs were $25,362 ($31,549) (Figure 5). Among all cohorts, patients who received allogeneic SCT had the highest all-cause health care costs ($54,337 [$64,761]) and the highest LBCL-related health care costs ($35,461 [$44,411]). Patients who received any SCT had significantly higher PPPM LBCL-related inpatient costs ($22,575 vs $4305, $P < 0.001$) but significantly lower outpatient costs ($4444 vs $9227, $P = 0.001$) than patients who did not receive an SCT. Mean (SD) PPPM all-cause costs were $46,174 ($49,057) for patients with SCT and $45,780 ($52,813) for patients without SCT.

DISCUSSION

The findings of this analysis provide insight into real-world treatment patterns, adverse events, health care resource utilization, and costs in patients with LBCL whose second-line treatment suggests that they were intended to receive SCT. Only 16.4% of patients with LBCL received an identifiable second-line therapy; among them, 21.1% received NCCN-recommended SCT-intended regimens. Overall, one-third of patients with an identifiable second-line therapy were eligible for SCT, but only 17.0% received SCT. Notably, only 22.7% of patients who received an SCT-preparative regimen in second-line therapy received SCT. These findings highlight substantial unmet needs in the



	All SCT Eligible (n=188)	Received any SCT (n=96)	Did not receive SCT (n=92)	ASCT (n=59)	Allo-SCT (n=37)
Outpatient pharmacy	$1332	$1288	$1377	$1220	$1398
Outpatient	$18,176	$13,686	$22,863††	$13,066	$14,674
Inpatient	$26,473	$31,200	$21,540	$26,769	$38,266



	All SCT Eligible (n=188)	Received Any SCT (n=96)	Did not receive SCT (n=92)	ASCT (n=59)	Allo-SCT (n=37)
Outpatient chemotherapy*	$4943	$2699	$7285 ††	$2687	$2719
Outpatient	$6784	$4444	$9227 ††	$4352	$4590
Inpatient	$13,635	$22,575	$4,305 ††	$19,078	$28,152

Figure 5. Mean monthly all-cause (A) and large B-cell lymphoma (LBCL)–related (B) health care costs during the second-line treatment window.

*Includes both outpatient pharmacy claims (National Drug Codes) as well as office-administered medication claims (Healthcare Common Procedure Coding System) for chemotherapy, mesna, rituximab, and corticosteroids. Statistical comparisons were made between patients who received SCT and those who did not received SCT and between patients who received autologous SCT and those who received allogeneic SCT. Allo-SCT = allogeneic SCT; ASCT = autologous SCT; PPPM = per patient per month; SCT = stem cell transplant.

†$P \leq 0.05$.

‡$P \leq .001$.

relapsed/refractory LBCL population. In particular, the fact that only a few patients who received SCT-intended therapy actually received SCT suggests that chemosensitivity in the post-rituximab era is a barrier to potentially curative treatment. Prior real-world studies on DLBCL, which report that 10% to 18% of patients received a second-line therapy and 8% to 25% of those received an SCT, indicate that these findings are not unique and confirm this treatment gap.[18–21,30] Also notable, among the 96 patients with SCT during the second-line treatment window, 38.5% received allogeneic SCT, which is a higher proportion than rates historically reported in second-line therapy LBCL populations. A recent study, for example, reported that 93% of the patients with DLBCL who received an SCT during second-line therapy received autologous SCT.[30]

The observed pattern of adverse events illustrates one of the important clinical consequences of the treatment patterns observed in the study population. Among the 188 patients in our study who were eligible for SCT, febrile neutropenia, anemia, thrombocytopenia, and nausea or vomiting were the most common treatment-related adverse events between the start of second-line therapy and the start of third-line therapy. The most common treatment-related adverse events were similar in type and incidence between patients with and without SCT, suggesting treatment-related adverse effects may be related more to drug therapy than to receipt of SCT.

Although rates of treatment-related adverse events were similar between patients who did or did not receive SCTs, we were not able to measure the severity of these adverse events. Because these patients were intended for SCT but did not receive SCT, a hypothetical reason could be that they might have experienced a severe adverse event that disqualified the patient from receipt of SCT and increased the non–LBCL-related costs. Future studies will be needed to examine this and other potential reasons why many SCT-intended patients do not receive SCT.

Mean PPPM all-cause total costs were similar between patients with and without SCT ($46,174 and $45,780, respectively). Although mean total costs between second- and third-line therapy were higher

for patients receiving SCTs, SCTs appeared to allow patients to go a longer time without additional treatment and/or to reduce the need for a third-line therapy. This longer second-line treatment window for patients receiving SCTs provided a longer time during which to amortize all-cause costs, which resulted in a fairly similar PPPM cost for patients with and without SCT. In addition, patients who received SCTs tended to be younger and healthier than those who do not receive SCTs,[18,20,21] which may partially explain the higher non–LBCL-related costs among the latter cohort. The LBCL-related costs PPPM were higher for patients with SCTs than for patients without SCTs ($29,718 vs $20,817, $P = 0.05$), most likely because of the cost of the SCT ($21,233) compared with other LBCL treatments.

The existing literature on costs is limited to the DLBCL population and uses older data and thus may not reflect more recent treatment patterns or costs. Different methods used to evaluate costs in previous studies also make direct comparisons difficult. Three recent studies reported costs among treated patients with DLBCL.[19,20,30] In one study that used the Optum database (2007–2015), mean (SD) monthly costs for patients with DLBCL were $14,402 ($10,951) during the first year after the DLBCL diagnosis.[19] Costs were likely lower in that study because they included all treated patients, even those cured by their first-therapy regimen, whereas the present study focused exclusively on patients with relapsed or refractory disease and costs accumulated during second-line therapy until the start of third-line therapy or end of the follow-up when there was no third-line therapy (mean, 406 days). In the second study using the MarketScan Commercial and Supplemental Databases (2006–2015), mean (SD) monthly costs in the first year after starting second-line therapy for patients with relapsed or refractory DLBCL were $25,189 ($14,527) among patients who received an SCT in second-line therapy and $14,577 ($13,267) among patients who did not receive an SCT in second-line therapy.[20] However, this second study was restricted to patients with at least 1 year of follow-up and therefore excluded high-cost patients who died as a result of disease progressions, adverse events, or other causes. In the third study, which also used the MarketScan Commercial and Medicare Supplemental Databases (2011–2017), the mean monthly costs were $32,857 during second-line therapy and $43,854 during third-line therapy.[30]

In our study, mean (SD) costs for an SCT were $187,235 ($116,706) for autologous SCT and $219,338 ($206,352) for allogeneic SCT. The reported costs of SCT vary greatly, with the variations driven to some extent by differences in characteristics of patient populations, timing of the study, use of charges or paid amounts, and the operational definition used for SCT-related costs. Our estimates may differ from other published estimates because they reflect only the cost of the SCT procedure, and as previous researchers have concluded, pre-transplant care is costly and costs vary considerably, depending on the type of conditioning regimen used[31,32] and the time horizon used to capture pre-transplant and post-transplant costs.[33] Previous studies appear to have generally used broader definitions of SCT-related costs and have reported that an autologous transplant was less expensive than an allogeneic transplant.[22,32,34,35] In recent reports, the mean paid costs of an inpatient admission for autologous SCT have ranged from $69,140 among adults with non-Hodgkin lymphoma in the National Inpatient Sample to $118,453 among adults with any hematologic or bone marrow cancer in the MarketScan database, whereas costs for allogeneic SCT have ranged from $118,378 to $259,749.[22,32,33] A cost of $114,500 has also been used for autologous SCT in a recent cost-effectiveness analysis.[36] Some researchers have estimated the first-year costs of allogeneic SCT at >$455,700, whereas others have estimated the total per patient costs, including pre-transplant care through 180 days after discharge from the transplant hospitalization, as $429,000 for autologous SCT and $934,000 for allogeneic SCT.[33] Inflating published cost estimates to 2020 US dollars suggests that the mean cost of autologous SCT would be approximately $182,000[31] and the mean cost of allogeneic SCT would be approximately $305,000.[32]

There are several limitations that need to be kept in mind when interpreting the results of this study, as with all claims data analysis. First, the potential for misclassification of covariates or study outcomes is present because patients were identified through administrative claims data as opposed to medical records. As with any claims database, the MarketScan Research Databases rely on administrative claims data for clinical detail. These data are subject to data-coding limitations and data entry errors. In particular, the code sets and diagnostic subtyping used to define LBCL and DLBCL in the literature is highly

variable. Although most of the comparative real-world data studies self-define their topic as DLBCL not LBCL, the code sets used to identify patients are not consistent regardless of whether they used ICD-CM or ICD-Oncology codes.[1,16–21,30] In addition, studying adverse events using claims data provides challenges, and it is possible that greater clinical detail and additional insights might be gained from examining patients' medical records. A strength of this study is its focus on the common adverse events reported in the ORCHARRD and CORAL studies, although we acknowledge that this is not exhaustive of all potential treatment-related adverse events that this population may experience. Because claims data do not include physician attribution of adverse events to a specific treatment, we took an inclusive approach in which all instances of relevant adverse event codes were considered evidence of adverse events. SCT-related adverse events, such as graft-versus-host disease, are not examined because it is not part of the study objectives. We also note that claims data lack the clinical specificity and granularity necessary to accurately differentiate between relapse and refractory disease; therefore, this distinction was not made. Second, this study was limited to only those individuals with commercial health coverage or private Medicare supplemental coverage. Consequently, the results of this analysis may not be generalizable to patients with other insurance or without health insurance coverage. Third, claims data can only identify whether a patient has filled a prescription. They do not include information on whether and how a patient uses the prescription. Fourth, information on drugs used during hospitalizations is not available in claims data. As a result, patients who received chemotherapy in the inpatient setting may have been mischaracterized as having a second-line regimen not intended for SCT.

CONCLUSIONS

In this real-world study, treatment patterns among patients with relapsed or refractory LBCL eligible for SCT were varied, but it is striking to see that only 22.7% of patients who received an SCT-preparative regimen actually received SCT. In other words, despite the availability of potentially curative therapy, most patients with relapsed or refractory LBCL who receive a preparatory second-line regimen do not receive SCTs and therefore cannot attain the important clinical benefits of that procedure. Of importance, the occurrence of treatment-related adverse events in second-line therapy did not vary by SCT status, and despite the upfront cost of SCT, when normalized across the second-line treatment window, all-cause costs PPPM were comparable between patients who did and did not receive an SCT. On the whole, these findings indicate that many patients with relapsed or refractory LBCL who are candidates for SCTs do not receive that potentially life-saving treatment and that patients who receive SCTs have similar select adverse events potentially related to systemic treatment and cost experiences during second-line therapy. The observed cost patterns in this study provide the important insight that despite higher initial costs for SCT, the mean PPPM costs are similar for patients with and without SCTs, a finding that coupled with the treatment patterns analysis suggests that SCT may allow patients to enjoy longer periods between treatments or possibly even reduce the need for third-line therapy. More broadly, these results indicate that in addition to their clinical benefits, potentially curative therapies, such as SCT, may offer economic benefits by preventing or delaying the need for subsequent treatment.

DECLARATION OF INTEREST

Drs. Snider and Cheng are employees of Kite, a Gilead Company. Ms. McMorrow, Dr. Song, and Mr. Diakun are employees of IBM Watson Health. Ms. Wade is an employee of Wade Outcomes Research and Consulting. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Medical writing services were provided by Jessamine Winer-Jones of IBM Watson Health. Drs. Snider and Cheng contributed to the study concept and design, data interpretation, manuscript preparation, and critical review. Ms. McMorrow, Dr. Song, and Mr. Diakun contributed to the study design, data analysis, data interpretation, manuscript preparation and critical review. Ms. Wade contributed to methodology, supervision, writing, review, and editing.

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APPENDIX

Table S1. Medications used to construct LOTs.

Per the NCCN Clinical Practice Guidelines for Large B-Cell Lymphoma, V5.2019		
Bendamustine	Doxorubicin	mitoxantrone
brentuximab vedotin	doxorubicin liposome	oxaliplatin[a]
carboplatin[a]	Etoposide	procarbazine
cisplatin[a]	Gemcitabine	rituximab
cyclophosphamide	Ifosfamide	vincristine
Cytarabine	lenalidomide	vinorelbine
Anthracycline therapies included in LOT1 construction but not in the NCCN guidelines		
Daunorubicin	Epirubicin	idarubicin

LOT: line of therapy

[a] Platinum-based therapies included in LOT2 although they are not included in the NCCN guidelines for SCT-intended LOT2 regimens.

Table S2. Treatment Patterns LOT3 Chemotherapy; SCT and CAR T after LOT2.

	All SCT eligible Patients		Received any SCT		Did not receive SCT		P value
	N=188		N=96		N=92		
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	
Receipt of LOT3 Chemotherapy (N, %)	63	33.5%	21	21.9%	42	45.7%	<0.001
Time (days) from start of LOT2 to LOT3 Chemotherapy (Mean, SD)	219.9	206.9	372.3	187.7	143.7	172.4	<0.001
SCT and CAR T from start of LOT2 to end of follow-up (N, %)							
Receipt of any SCT from start of LOT2 through end of follow-up	96	51.1%	96	100.0%			
Receipt of Autologous SCT	59	31.4%	59	61.5%			
Receipt of Allogeneic SCT	37	19.7%	37	38.5%			
Receipt of CAR T from start of LOT2 through end of follow-up	14	7.4%	7	7.3%	7	7.6%	<0.001

LOT: line of therapy; SCT: stem cell transplant; CAR T: chimeric antigen receptor T-cell therapy.