The Oncologist®

Health Outcomes and Economics of Cancer Care

Direct Costs Associated with Relapsed Diffuse Large B-Cell Lymphoma Therapies

Anna Purdum,[a] Ryan Tieu,[b] Sheila R. Reddy,[b] Michael S. Broder[b]

[a]Kite Pharma, Inc., Santa Monica, California, USA; [b]Partnership for Health Analytic Research, LLC, Beverly Hills, California, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

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Abstract

Background. About one third of patients with diffuse large B-cell lymphoma (DLBCL) relapse after receiving first-line (1L) treatment of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Relapsed patients may then be eligible for second-line (2L) therapy. The study's objective was to examine health care use and costs among treated patients with DLBCL receiving 2L therapy versus those without relapse.

Materials and Methods. We analyzed Truven Health MarketScan® claims data between 2006 and 2015. Patients (≥18 years of age) had ≥1 DLBCL claim from 1 year before to 90 days after beginning 1L therapy, and comprised those without 2L treatment for ≥2 years (cured controls) versus those who initiated non-R-CHOP chemotherapy after discontinuing 1L therapy (2L cohort). 2L patients were further subgrouped: hematopoietic stem cell transplant (HSCT [yes/no]) and time of relapse (months between 1L and 2L): early (≤3), mid (4–12), and late (>12) relapse. The primary outcome was 1- and 2-year health care costs. Hospitalization rate and length of stay were also measured.

Results. A total of 1,374 patients with DLBCL received R-CHOP and fulfilled all criteria: 1,157 cured controls and 217 2L patients (87 early-relapse, 66 mid-relapse, 64 late-relapse). Twenty-eight percent of 2L patients received HSCT. Charlson Comorbidity Index/mortality risk was higher for 2L patients (4.2 [SD: 3.0]) versus controls (3.8 [2.6]; $p = .039$), as were yearly costs (Year 1: $210,488 [$172,851] vs. $25,044 [$32,441]; $p < .001$ and Year 2: $267,770 [$266,536] vs. $42,272 [$49,281]; $p < .001$). HSCT and chemotherapy were each significant contributors of cost among 2L patients.

Conclusion. DLBCL is resource intensive, particularly for 2L patients. Great need exists for newer, effective therapies for DLBCL that may save lives and reduce costs. ***The Oncologist*** 2019;24:1–8

Implications for Practice: This study identified multiple important drivers of cost in the understudied population of patients with diffuse large B-cell lymphoma (DLBCL) receiving second-line (2L) treatment. Such drivers included hematopoietic stem cell transplant (HSCT) and chemotherapy. Even though HSCT is currently the only curative therapy for DLBCL, less than one third of patients receiving 2L and subsequent treatment underwent transplant, which indicates potential underuse. The variation in chemotherapy regimens suggested a lack of consensus for best practices. Further research focusing on newer and more effective treatment options for DLBCL has the potential to decrease mortality, in addition to reducing the extensive costs related to therapy options such as transplant.

Introduction

Diffuse large B-cell lymphoma (DLBCL), a type of non-Hodgkin's lymphoma (NHL), accounts for approximately 30% of all NHL cases and is the most common lymphoid neoplasm in adults [1, 2]. Survival for patients with DLBCL was poor before the introduction of the current standard first-line (1L) regimen of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); with R-CHOP, survival is 74.3% at 6 years [3].

About 20%–50% of patients with DLBCL relapse or become refractory to 1L therapy [4, 5], some of whom may be eligible for second-line and subsequent (2L+) treatment, such as hematopoietic stem cell transplant (HSCT) or chemotherapy. Approximately 50% of relapsed patients are eligible to undergo transplant, and half of those respond to salvage therapy and proceed to transplant [4]. For patients with

Correspondence: Anna Purdum, Pharm.D., Kite Pharma, Inc., 2225 Colorado Ave., Santa Monica, California 90404, USA. Telephone: 424-532-5062; e-mail: apurdum@kitepharma.com Received August 10, 2018; accepted for publication January 4, 2019. http://dx.doi.org/10.1634/theoncologist.2018-0490

relapsed disease, HSCT is considered potentially curative 2L+ therapy; however, long-term survival is generally limited to those with chemosensitive disease. Progression-free survival at 3 years is 40% among patients with HSCT; thus, only 10% of the relapsing patients are ultimately cured [4]. Within 3 years, 60% of patients receiving HSCT relapse. For patients who become refractory to chemotherapy, the median survival is 6.3 months [5].

The goal of 1L treatment for patients with DLBCL is curative therapy. However, many people do relapse, and when they do, it can be quite expensive. By estimating the magnitude of cost and what determines it, we can better understand the incremental economic burden of patients who relapse relative to those who do not.

This study used a retrospective analysis of insurance claims data to examine use and costs associated with treating patients with DLBCL who had progressed beyond 1L therapy compared with those who had not relapsed.

Materials and Methods

We conducted a retrospective analysis using Truven Health MarketScan® patient-level insurance claims data from 2006 to 2015 to determine the direct cost of illness for patients diagnosed with DLBCL who received and later progressed beyond 1L R-CHOP therapy.

MarketScan is a large administrative claims database of employer-sponsored health insurance in the U.S. The database contains information on enrollment and benefits, patient demographics, inpatient and outpatient services and costs, and outpatient pharmacy data. Information on diagnoses and procedures (i.e., International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] diagnosis codes and Current Procedural Terminology 4 and ICD-9-CM procedure codes) are reported on administrative claims in the outpatient and inpatient settings. As U.S. implementation of ICD-10-CM (i.e., ICD 10th Revision) began in October 2015, near the end of the study period, ICD-10-CM diagnosis codes were not used in this study. Data on prescription drug dispensing (e.g., National Drug Codes, fill dates, days of drug supply) are reported on claims generated through outpatient pharmacies.

The study population comprised patients who were at least 18 years of age who had received R-CHOP as 1L therapy and a claim for DLBCL (ICD-9-CM 200.7X) in the year before or 90 days after the start of 1L therapy. Among identified patients with DLBCL and 1L R-CHOP therapy, we created two study cohorts: patients who had no 2L treatment for at least 2 years (cured controls), and patients who initiated non-R-CHOP chemotherapy after discontinuing 1L therapy (2L+ patients). Discontinuation of therapy was defined as a gap in use of at least 60 days. Because the primary goal of the study was to characterize the cost of treatment among patients treated with 2L or beyond, controls served to provide an anchor for costs observed in the 2L+ cohort.

The index date was defined as the end of 1L therapy for controls and the start of 2L treatment among 2L+ patients. Patients who were not continuously enrolled in a health plan for 6 months before and at least 1 year after the index date were excluded. In addition, we excluded 2L+ patients who restarted R-CHOP as 2L therapy and controls who were treated with rituximab or lenalidomide monotherapy (this treatment might have represented maintenance as opposed to active therapy [6]).

To understand the association between costs and both HSCT and timing of relapse, we further subgrouped 2L+ patients based on whether HSCT was received (yes/no) and on time between the end of 1L and start of 2L treatment: early- (≤3 months), mid- (4–12 months), and late-relapse (>12 months).

Our primary outcome was health care costs, which we measured using the amount paid, or fee-for-service equivalent, field in the claims. We computed the mean costs for total health care including inpatient services, outpatient office visits, outpatient hospital (including emergency department) visits, pharmacy services, and chemotherapy. Costs were calculated for 1 and 2 years (cumulative) following index treatment. To account for potential changes in the cohort composition beyond the first year of follow-up due to disenrollment or death that would affect costs, we examined unadjusted year 1, year 2, and year 3 costs (all noncumulative) according to patient enrollment length. Other measures included 1-year hospitalization rate, mean length of stay (LOS), and HSCT rate.

Baseline measures included age, sex, geographic region, payment source (commercial vs. Medicare), Charlson Comorbidity Index (CCI) [7, 8], which captures mortality risk, and the number of chronic conditions, counted using the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project Chronic Condition Indicator for ICD-9-CM [9].

Descriptive statistics including means, SDs, medians for continuous data, and relative frequencies and percentages for categorical data were reported for the use and cost measures compared between study groups. Generalized linear models were used to adjust cost. We reported the least squares adjusted mean 1-year and 2-year costs, controlling for age group, sex, region, and CCI. Comparisons between response types were further adjusted for HSCT in the first year after the start of 2L treatment. Comparisons between HSCT statuses were further adjusted for response type. Because of small sample size, we do not intend to make statistical inference based on the model results. *p* values were not adjusted for multiplicity and should be considered nominal.

Health care costs were adjusted to 2015 U.S. dollars based on the Consumer Price Index for Health Services [10]. All data transformations and analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC).

Results

We identified 6,107 patients with evidence of R-CHOP treatment in the claims (Fig. 1), of whom 1,632 had a previous diagnosis of DLBCL and were continuously enrolled for at least 6 months prior to and 2 years after R-CHOP initiation. From this group, we derived our final cohort, which comprised 217 patients who initiated a 2L+ treatment (2L+ cohort) and 1,157 cured controls who completed 1L treatment and did not use subsequent therapy. Within the 2L+ cohort, 87 patients were classified as having relapsed early, 66 having

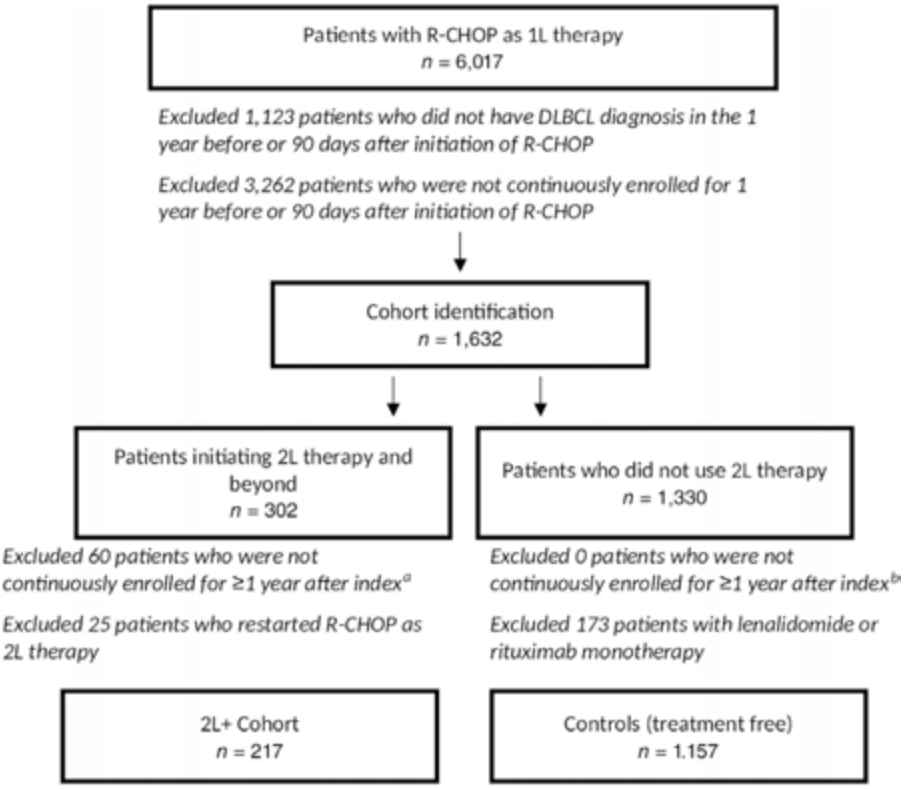

Figure 1. Patient identification. After applying study criteria, the final sample size included 217 patients who initiated a 2L+ treatment (2L+ cohort) and 1,157 treatment-free patients (controls). [a]Index date for 2L patients was the start of their 2L treatment. [b]Index date for controls was 60 days after the end of 1L treatment.
Abbreviations: 1L, first-line treatment; 2L+, second-line and subsequent treatments; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

mid-relapse, and 64 relapsing late. Most 2L+ patients did not receive a transplant (n = 156); however, some did (n = 61).

Patient Characteristics

Patient characteristics are presented in Table 1. The mean (SD) age among 2L+ patients was 58.3 (14.1) years compared with 60.8 (14.4) years for controls (p = .020). These groups were predominantly male (2L+, 58.5% vs. controls: 53.2%, p = .152) and covered by commercial insurance (2L+, 68.7% vs. controls: 61.9%, p = .058). Patients represented all regions of the U.S., although small differences between groups were statistically significant (p = .017). Although 2L patients and controls had a similar burden of chronic conditions (4.7 [1.9] vs. 4.6 [1.9] conditions, respectively; p = .370), 2L patients appeared to have increased risk of mortality compared with controls according to the CCI (4.2 [3.0] vs. 3.8 [2.6]; p = .039). The mean (SD) follow-up time was 1,094 (589.1) days for 2L+ patients compared with 1,358 (664.0) days for controls (p < .001).

For the subgroups based on relapse type and HSCT status, differences in characteristics were generally difficult to detect because of small sample sizes within the groups. However, early-relapse patients were on average younger than mid- and late-relapse patients (55.5 [15.8] vs. 58.3 [13.5] vs. 62.1 [11.4] years, respectively; p = .014) and had more chronic conditions (5.5 [1.8] vs. 4.5 [1.8] vs. 3.9 [1.7] conditions, respectively; p < .001). Patients who underwent HSCT were younger than those who did not (54.7 [10.9] vs. 59.7 [15.0] years, respectively; p = .007), and were more often commercially insured (83.6% vs. 62.8%; p = .003).

Health Care Use

In the main analysis, 79.7% of 2L+ patients had a hospitalization compared with 15.2% of controls with a mean (SD) LOS of 23.1 (22.0) and 7.4 (12.6) days, respectively (p < .001; Table 2). Twenty-eight percent of 2L+ patients had an HSCT versus none of the controls (by definition; p < .001). Within the subgroup of 2L+ patients, mid-relapse patients compared with early- and late-relapse patients had a numerically higher rate of hospitalization (83.3% vs. 78.2% vs. 78.1%; p = .682), longer LOS (28.2 [26.3] vs. 19.5 [17.4] and 22.3 [21.9] days; p = .089), and higher rate of HSCT (39.4% vs. 23.0% vs. 23.4%; p = .050); however, differences were not statistically significant. Patients who underwent HSCT had higher rates of hospitalization (100% vs. 71.8%; p < .001) and longer LOS (32.3 [17.5] vs. 12.9 [20.9] days; p < .001) than those who did not have a transplant.

Unadjusted Costs

Second-line patients had a mean (SD) total cost of $210,488 ($172,851) in the first year after starting 2L therapy, whereas total cost was $25,044 ($32,441) among controls (p < .001; Table 2). In 2L+ patients, mean (SD) inpatient costs were $90,882 ($109,480), of which $23,743 was chemotherapy related. This compares with a mean (SD) inpatient cost of $4,421 ($16,602; p < .001) in controls. In 2L patients, mean (SD)

Table 1. Patient demographics and comorbidities

	2L+ vs. controls			Relapse type				HSCT status		
Demographics and comorbidities	**2L+ cohort, *n* = 217**	**Controls, *n* = 1,157**	***p* value**	**Early relapse, *n* = 87**	**Mid relapse, *n* = 66**	**Late relapse, *n* = 64**	***p* value**	**HSCT, *n* = 61**	**No HSCT, *n* = 156**	***p* value**
Age, years, mean (SD)	58.3 (14.1)	60.8 (14.4)	.020	55.5 (15.8)	58.3 (13.5)	62.1 (11.4)	.014	54.7 (10.9)	59.7 (15.0)	.007
Female, *n* (%)	90 (41.5)	541 (46.8)	.152	42 (48.3)	22 (33.3)	26 (40.6)	.176	20 (32.8)	70 (44.9)	.104
Region, *n* (%)			.017				.452			.862
Midwest	69 (31.8)	392 (33.9)		26 (29.9)	19 (28.8)	24 (37.5)		20 (32.8)	49 (31.4)	
Northeast	51 (23.5)	190 (16.4)		25 (28.7)	14 (21.2)	12 (18.8)		13 (21.3)	38 (24.4)	
South	74 (34.1)	379 (32.8)		25 (28.7)	28 (42.4)	21 (32.8)		20 (32.8)	54 (34.6)	
West	23 (10.6)	196 (16.9)		11 (12.6)	5 (7.6)	7 (10.9)		8 (13.1)	15 (9.6)	
Payment source, *n* (%)			.058				.633			.003
Commercial	149 (68.7)	716 (61.9)		61 (70.1)	47 (71.2)	41 (64.1)		51 (83.6)	98 (62.8)	
Medicare	68 (31.3)	441 (38.1)		26 (29.9)	19 (28.8)	23 (35.9)		10 (16.4)	58 (37.2)	
Days of follow-up, mean (SD)	1,094 (589.1)	1,358 (664.0)	<.001	1,229 (529.1)	918.2 (581.1)	1,093 (633.7)	.005	1,124 (621.7)	1,083 (577.5)	.647
Charlson Comorbidity Index, mean (SD)	4.2 (3.0)	3.8 (2.6)	.039	5.0 (3.6)	3.6 (2.6)	3.8 (2.3)	.007	3.6 (2.6)	4.5 (3.2)	.051
Number of chronic conditions, mean (SD)[a]	4.7 (1.9)	4.6 (1.9)	.370	5.5 (1.8)	4.5 (1.8)	3.9 (1.7)	<.001	4.0 (1.6)	5.0 (2.0)	<.001

[a]Agency for Healthcare Research and Quality. HCUP Chronic Condition Indicator. Healthcare Cost and Utilization Project (HCUP). www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. Published May 2016.
Abbreviations: 2L+, second-line and subsequent treatments; HSCT, hematopoietic stem cell transplant.

outpatient costs were $109,525 ($92,980), of which $23,280 was for chemotherapy. In controls, outpatient costs were $17,686 ($19,850; $p < .001$; with no chemotherapy costs by definition). Two-year cumulative mean (SD) costs were $267,770 ($266,536) for 2L+ patients compared with $42,272 ($49,281) for controls ($p < .001$).

Findings based on timing of relapse showed higher mean total costs in the first year of 2L therapy among mid-relapse patients compared with late-relapse and early-relapse patients; however, the differences were not statistically significant. The total 2-year costs were also higher among mid-relapse compared with early- and late-relapse patients although again without statistical significance ($p = .950$).

Patients who underwent HSCT had considerably higher 1-year and 2-year mean (SD) total costs compared with those who did not have a transplant (1-year: $301,426 [$174,320] vs. $174,928 [$159,203], $p < .001$; 2-year: $421,739 [$363,498] vs. $205,618 [$183,901], $p < .001$). Comparing disaggregated costs between patients with versus those without HSCT, we observed significant differences in 1-year inpatient costs ($168,998 [$102,761] vs. $60,337 [$96,305]; $p = .019$), cost of HSCT ($126,030 [$74,052] vs. $0 [0]; $p < .001$), outpatient hospital visits ($85,269 [$88,945] vs. $59,345 [$78,673]; $p = .037$), and pharmacy costs ($14,345 [$15,436] vs. $8,413 [$12,953]; $p = .005$). Group differences for 2-year disaggregated costs were generally similar.

Adjusted Costs

In the adjusted analyses, 2L+ patients had a mean (95% confidence interval) total cost of $208,300 (198,396–218,204) in the first year compared with $25,454 (21,189–29,719; $p < .001$) among controls, adjusting for age group, sex, region, and CCI (Table 3). This large difference in adjusted costs between 2L+ patients and controls persisted over 2 years ($257,822 [260,872–290,772] vs. $43,092 [36,654–49,530]; $p < .001$). Mean total 2-year costs were substantially higher than 1-year costs among all relapse groups, albeit differences between the groups were not statistically significant likely due to very small sample sizes. Adjusting for timing of relapse and other key variables, the mean total first-year costs for patients with HSCT were much higher compared with cost in those without a transplant ($282,022 [241,594–322,450] vs. $182,516 [157,803–207,229]; $p < .001$). This difference in total costs was nearly doubled over 2 years ($409,778 [333,259–486,296] vs. $210,446 [163,258–257,635]; $p < .001$).

Cost over Time

The analysis of cost over time showed that mean total costs varied by enrollment length and were lower for patients with longer enrollment ($233,593 vs. $229,566 vs. $172,937; Table 4). For patients with 2 and 3 years of enrollment, total costs were highest in the first year after initiating 2L treatment. Total costs persisted in years 2 and 3 among enrolled patients despite being lower than 1-year costs.

Discussion

This study examined the cost of illness for patients with DLBCL and found that DLBCL is resource intensive, particularly for patients who move beyond the 1L treatment. One-year costs among patients who initiated 2L+ therapy were more than eightfold those of controls. HSCT was a major driver of costs, despite less than one third (28%) of 2L+ patients having undergone the procedure. Patients who underwent HSCT had on average $126,000 in additional first-year costs compared with transplant-naïve patients; this difference grew to $143,000 over 2 years.

Table 2. Unadjusted 1-year and 2-year[a] health care use and costs

	2L+ vs. controls			Relapse type				HSCT status		
1-year costs	**2L+ cohort, *n* = 217**	**Controls, *n* = 1,157**	***p* value**	**Early relapse, *n* = 87**	**Mid relapse, *n* = 66**	**Late relapse, *n* = 64**	***p* value**	**HSCT, *n* = 61**	**No HSCT, *n* = 156**	***p* value**
Any inpatient hospitalization, *n* (%)	173 (79.7)	176 (15.2)	<.001	68 (78.2)	55 (83.3)	50 (78.1)	.682	61 (100.0)	112 (71.8)	<.001
Number of hospitalizations, mean (SD)	2.7 (2.6)	0.2 (0.6)	<.001	2.7 (2.4)	2.8 (2.8)	2.5 (2.7)	.854	3.3 (2.4)	2.4 (2.7)	.019
Hospitalization LOS, mean days (SD)	23.1 (22.0)	7.4 (12.6)	<.001	19.5 (17.4)	28.2 (26.3)	22.3 (21.9)	.089	32.3 (17.5)	12.9 (20.9)	<.001
HSCT within 1 year, *n* (%)	61 (28.1)	0 (0.0)	<.001	20 (23.0)	26 (39.4)	15 (23.4)	.050	—	—	
Total 1-year health care costs, mean $ (SD) [median]	210,488 (172,851) [160,483]	25,044 (32,441) [15,372]	<.001	191,079 (175,752) [130,929]	232,796 (164,914) [200,305]	213,866 (176,517) [161,465]	.331	301,426 (174,320) [238,032]	174,928 (159,203) [116,223]	<.001
Inpatient costs, mean $ (SD)	90,882 (109,480)	4,421 (16,602)	<.001	83,345 (107,479)	109,865 (114,420)	81,551 (106,176)	.240	168,998 (102,761)	60,337 (96,305)	.019
Chemotherapy[b]	23,743 (41,911)	0.0 (0.0)	<.001	25,395 (43,613)	23,498 (44,608)	21,750 (36,945)	.869	26,771 (38,681)	22,559 (43,169)	.507
Cost of HSCT[b]	35,428 (68,905)	0.0 (0.0)	<.001	32,104 (76,278)	49,933 (74,121)	24,987 (48,182)	.100	126,030 (74,052)	0.0 (0.0)	<.001
Outpatient costs, mean $ (SD)	109,525 (92,980)	17,686 (19,850)	<.001	98,553 (88,696)	112,076 (85,710)	121,810 (104,862)	.306	118,083 (96,783)	106,178 (91,551)	.398
Office visits	34,035 (44,972)	5,405 (6,437)	<.001	$31,802 (44,972)	$33,682 (40,102)	$37,433 (44,135)	.748	26,813 (31,932)	36,858 (48,940)	.078
Hospital visits	66,632 (82,313)	10,089 (16,380)	<.001	59,963 (82,632)	69,464 (77,462)	72,778 (100,525)	.607	85,269 (88,945)	59,345 (78,673)	.037
ED visits	529 (3,081)	267 (1,783)	.225	405 (1,022)	848 (5,402)	369 (919)	.602	306 (609)	616 (3,613)	.302
Other outpatient visits	8,329 (27,631)	1,925 (7,058)	<.001	6,382 (15,279)	8,081 (34,528)	11,230 (32,480)	.567	5,694 (9,599)	9,359 (32,007)	.199
Chemotherapy	23,280 (30,220)	0.0 (0.0)	<.001	21,366 (27,602)	22,361 (26,554)	26,828 (36,672)	.526	18,088 (23,766)	25,309 (32,237)	.072
Pharmacy costs, mean $ (SD)	10,081 (13,919)	2,937 (7,776)	<.001	9,182 (13,286)	10,854 (14,693)	10,505 (14,092)	.733	14,345 (15,436)	8,413 (12,953)	.005
Chemotherapy	220 (1,108)	0.0 (0.0)	<.001	92 (676)	499 (1,742)	105 (583)	.048	69 (436)	279 (1,275)	.073

	2L+ vs. controls			Relapse type				HSCT status		
2-year costs	**2L+ cohort, *n* = 153**	**Controls, *n* = 961**	***p* value**	**Early relapse, *n* = 83**	**Mid relapse, *n* = 33**	**Late relapse, *n* = 37**	***p* value**	**HSCT, *n* = 44**	**No HSCT, *n* = 109**	***p* value**
Total 2-year health care costs, mean $ (SD) [median]	267,770 (266,536) [186,944]	42,272 (49,281) [28,059]	<.001	264,900 (300,924) [150,421]	280,876 (229,577) [212,968]	262,520 (215,949) [225,218]	.950	421,739 (363,498) [291,944]	205,618 (183,901) [145,895]	<.001
Inpatient costs, mean $ (SD)[b]	105,503 (144,188)	7,047 (27,326)	<.001	106,511 (165,722)	115,131 (121,291)	94,655 (109,263)	.837	215,860 (183,414)	60,956 (94,348)	<.001
Chemotherapy[b]	23,416 (42,551)	0.0 (0.0)	<.001	26,969 (47,709)	17,667 (32,859)	20,575 (37,850)	.513	33,635 (48,732)	19,291 (39,280)	.059
Cost of HSCT[b]	40,981 (82,861)	0.0 (0.0)	<.001	37,177 (91,727)	60,487 (85,098)	32,118 (54,080)	.299	142,504 (97,296)	0.0 (0.0)	<.001

(continued)

Table 2. (continued)

2-year costs	2L+ vs. controls			Relapse type				HSCT status		
	2L+ cohort, *n* = 153	Controls, *n* = 961	*p* value	Early relapse, *n* = 83	Mid relapse, *n* = 33	Late relapse, *n* = 37	*p* value	HSCT, *n* = 44	No HSCT, *n* = 109	*p* value
Outpatient costs, mean $ (SD)	145,952 (144,548)	29,462 (30,788)	<.001	143,042 (154,205)	144,979 (123,412)	153,347 (142,973)	.937	183,686 (200,214)	130,720 (112,393)	.104
Office visits	$43,281 (62,029)	9,220 (10,997)	<.001	43,275 (67,993)	36,092 (44,425)	49,704 (62,219)	.660	34,697 (46,986)	46,746 (67,037)	.210
Hospital visits	88,871 (112,723)	16,476 (25,229)	<.001	88,348 (117,193)	90,887 (105,264)	88,244 (111,857)	.993	134,977 (156,296)	70,259 (83,315)	.012
ED visits	847 (2,270)	525 (2,924)	.120	1,124 (2,876)	452 (1,069)	577 (1,225)	.253	662 (1,393)	921 (2,541)	.421
Other outpatient visits	13,022 (41,955)	3,241 (9,868)	.004	10,414 (29,604)	17,558 (66,279)	14,826 (38,642)	.682	13,533 (34,846)	12,815 (44,652)	.924
Chemotherapy	29,024 (41,568)	0.0 (0.0)	<.001	29,375 (41,517)	18,645 (21,811)	37,495 (52,666)	.166	21,878 (31,860)	31,909 (44,705)	.122
Pharmacy costs, mean $ (SD)	16,315 (24,268)	6,840 (12,704)	<.001	15,346 (25,140)	20,766 (24,104)	14,518 (22,513)	.488	22,193 (28,035)	13,942 (22,275)	.057
Chemotherapy	935 (6,164)	0.0 (0.0)	<.001	913 (7,277)	1,853 (6,525)	164 (766)	.522	2,273 (10,938)	395 (2,196)	.265

[a]2-year health care costs measured as a subset of 1-year costs.
[b]Based on DRG indicators in claims. Specific charges for chemotherapy or HSCT cannot be identified through inpatient claims. Chemotherapy DRG includes associated procedures, drugs, and materials, etc., and in some instances, may include the cost related to HSCT (e.g., for conditioning regimens). Also, mean costs for HSCT include patients who did not have a transplant and thus have a value of $0.
Abbreviations: —, no data; 2L+, second-line and subsequent treatments; DRG, diagnosis-related group; ED, emergency department; HSCT, hematopoietic stem cell transplant; LOS, length of stay.

Table 3. Adjusted 1-year and 2-year[a] total health care costs[b]

Adjusted costs	2L+ vs. controls			Relapse type				HSCT status		
	2L+ cohort, *n* = 217	Controls, *n* = 1,157	*p* value	Early relapse, *n* = 87	Mid relapse, *n* = 66	Late relapse, *n* = 64	*p* value	HSCT, *n* = 61	No HSCT, *n* = 156	*p* value
Total 1-year costs, mean $ (95% CI)[a]	208,300 (198,396–218,204)	25,454 (21,189–29,719)	<.001	195,500 (161,782–229,218)	213,993 (175,587–252,400)	227,247 (188,072–266,421)	.487	282,022 (241,594–322,450)	182,516 (157,803–207,229)	<.001
	2L+ cohort, *n* = 153	Controls, *n* = 961	*p* value	Early relapse, *n* = 83	Mid relapse, *n* = 33	Late relapse, *n* = 37	*p* value	HSCT, *n* = 44	No HSCT, *n* = 109	*p* value
Total 2-year costs, mean $ (95% CI)[a]	257,822 (260,872–290,772)	43,092 (36,654–49,530)	<.001	270,013 (214,764–325,262)	240,295 (152,934–327,655)	287,244 (202,139–372,349)	.744	409,778 (333,259–486,296)	210,446 (163,258–257,635)	<.001

[a]2-year adjusted costs were performed for exploratory purposes, the results of which may not be interpretable because of insufficient sample size.
[b]Mean total health care costs adjusted by age group, sex, region, and Charlson Comorbidity Index. Comparisons between response types were further adjusted for HSCT in the first year after start of 2L treatment. Comparisons between HSCT statuses were further adjusted for response type.
Abbreviations: 2L+, second-line and subsequent treatments; CI, confidence interval; HSCT, hematopoietic stem cell transplant.

Chemotherapy was another important contributor to costs, accounting for more than one fifth of total health care costs. Chemotherapy regimens were varied and included dozens of antineoplastic agent combinations, suggesting that a standard of care did not prevail in our cohort. Similar findings were shown in a recent publication that demonstrated that approximately 43% of patients received therapies not classified by National Comprehensive Cancer Network guidelines in the relapse/refractory setting [11]. We also observed that mid-relapse patients had higher costs in the first year compared with late- and early-relapse patients, likely because of HSCT being more common in the former group. Adjusted analyses in which late-relapse patients became most costly in the first year pointed to this finding; however, small sample sizes prevented statistical inference.

These findings have two important implications for management of DLBCL. First, HSCT—the only curative therapy—may be underused, because less than one third of relapsed patients receive the procedure. Our findings are consistent with a prior study that suggests three fourths of patients are

Table 4. Cost over time among patients on 2L+ treatment

Total costs	Only 1 year enrollment 2L+ cohort, *n* = 64	2 years enrollment 2L+ cohort, *n* = 73	3 years enrollment 2L+ cohort, *n* = 79
Total costs in year 1, mean $ (SD)	233,593	229,566	172,937
	(174,946)	(198,500)	(139,009)
Total costs in year 2, mean $ (SD)	—	99,113	37,771
	—	(179,311)	(66,243)
Total costs in year 3, mean $ (SD)	—	—	37,486
	—	—	(57,842)

Abbreviations: —, no data; 2L+: second-line and subsequent treatments.

not offered a transplant because they are either unfit for a transplant or chemoresistant to salvage therapy and unable to receive a transplant [4]. Second, the advent of newer, effective therapies for relapsed/refractory DLBCL may save lives and may replace expensive transplants and other costly care, although if new therapies are more expensive than older ones, or used in a wider population (e.g., because of better efficacy), population costs may not decrease.

Previous research on the cost of DLBCL among 2L+ patients in the U.S. shows similar high expenditures, although among specific patient populations [12, 13]. A 2016 study of administrative claims found a mean total health care cost among allogeneic HSCT recipients of $455,741 in the year following transplant [12]. Costs decreased over time but remained high even 3 years after transplant ($72,957 [*n* = 11]). A Surveillance, Epidemiology, and End Results-Medicare study estimated 24-month total cost of $116,237 for relapsed and $97,154 for refractory 2L patients receiving outpatient chemotherapy [14]. Furthermore, other Medicare claims analyses show similar high costs among relapsed patients with average monthly costs ranging from $6,566 to $22,472 (about $78,000 to $269,000 per year) for beneficiaries with relapsed disease [14, 15].

We also found that costs were highest in the first year after initiation of 2L treatment for DLBCL but persisted over time into the second and third years. Costs over time varied by enrollment: Patients with longer enrollment had lower costs each year compared with those with shorter enrollment. We believe this pattern may be indicative of differences in health status and that patients with shorter enrollment may have had early deaths, consistent with survival studies [6, 16, 17], and therefore elevated costs in the last year of life. Our study adds to the literature by presenting a comprehensive picture of 2L+ costs among commercially insured patients with DLBCL and by determining the extent to which HSCT is a driver of 2L+ costs in this population.

Limitations

Our findings are limited by certain factors. First, we could not fully account for disease severity in our cost analysis, contributing to bias in our estimates. Second, we observed small sample sizes in the longer enrollment periods, thus making it difficult to infer about cost burden beyond the second year after initiation of 2L treatment. Third, we could not isolate inpatient chemotherapy in the inpatient claims from other, potentially unrelated (i.e., nonchemotherapy), services that occurred during the same inpatient stay, which may have led us to overestimate chemotherapy costs in the inpatient setting. Fourth, we studied only a subset of patients, both because our data represent patients with commercial insurance (and therefore may not be generalizable to populations that are not commercially insured) and because we were restricted to a group that had at least 2 years of enrollment following the initiation of 2L treatment. Subjects who changed employers or who died before 2 years would have been excluded. Furthermore, the lack of data on survival is a significant limitation of studies done using insurance claims data, as disenrollment and death cannot be reliably distinguished. Lastly, palliative radiation costs, which significant numbers of patients receive, were not included.

Conclusion

Our analysis demonstrated that DLBCL treatment beyond 1L is resource intensive with poor outcomes, and chemotherapy and HSCT are major drivers of cost despite a low rate of HSCT. Observed differences in costs for mid-relapse patients compared with late- or early-relapse patients are likely due to higher transplant rates. Future research that focuses on only patients with 2L+ treatment may result in a larger sample size and greater ability to detect cost differences within 2L+ patients over multiple years.

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Author Contributions

Conception/design: Anna Purdum, Ryan Tieu, Sheila R. Reddy, Michael S. Broder
Provision of study material or patients: Anna Purdum, Ryan Tieu, Sheila R. Reddy, Michael S. Broder
Collection and/or assembly of data: Anna Purdum, Ryan Tieu, Sheila R. Reddy, Michael S. Broder
Data analysis and interpretation: Anna Purdum, Ryan Tieu, Sheila R. Reddy, Michael S. Broder
Manuscript writing: Anna Purdum, Ryan Tieu, Sheila R. Reddy, Michael S. Broder
Final approval of manuscript: Anna Purdum, Ryan Tieu, Sheila R. Reddy, Michael S. Broder

Disclosures

Anna Purdum: Kite Pharma, Inc. (E); **Ryan Tieu:** Partnership for Health Analytic Research, LLC (E, C/A); **Sheila R. Reddy:** Partnership for Health Analytic Research, LLC (E); **Michael S. Broder:** Partnership for Health Analytic Research, LLC (E).

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