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SHORT COMMUNICATION

Examining the medical resource utilization and costs of relapsed and refractory chronic lymphocytic leukemia in Ontario

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ABSTRACT

Purpose The purpose of the present study was to collect medical resource utilization data and costs in Ontario for the management of patients with relapsed or refractory chronic lymphocytic lymphoma (CLL) who have undergone at least 1 treatment course and have been stratified by Rai staging.

Methods This retrospective longitudinal cohort study, conducted by chart review, analyzed anonymized patient records from two cancer centres in Ontario. Comprehensive records of 86 patients meeting the inclusion criteria were used to obtain resource utilization, which, multiplied by unit costs, were used to determine overall and mean costs. Descriptive statistics are presented for patient demographics, medical resource utilization, and costing data.

Results The total cost for the cohort was $2.2 million over a mean follow-up period of 4.7 years. The mean total cost per patient (regardless of follow-up) was $25,736. In terms of Rai staging, overall mean costs were highest for stage IV patients. Almost 50% of the total cost was attributable to CLL treatments, among which fludarabine-based treatments had the highest utilization.

Conclusions For this Canadian CLL cohort, medical resource utilization and costs were determined to be $2.2 million, with CLL treatments accounting for about half the cost. Costs generally increased with Rai stage.

Key Words Chronic lymphocytic leukemia, utilization, costs, Canada

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a form of leukemia characterized by neoplastic growth and proliferation of B lymphocytes in the peripheral blood, bone marrow, spleen, and lymph nodes[1]. The median age of onset ranges between 70 and 75 years[2]. A recent Canadian study described the underreporting of CLL cases in cancer registries and determined the prevalence of CLL to be 7.99 per 100,000 population[3]. According to the Canadian Cancer Society, approximately 2395 new cases of CLL were diagnosed in 2013 in Canada[4]. Risk factors for CLL include advanced age, sex, ethnicity, and exposure to herbicides or pesticides[5].

Chronic lymphocytic leukemia is often a slowly progressing disease, and treatment is usually delayed until symptomatic disease progression is observed. That approach can necessitate a long "watch and wait" period in which patients are monitored for symptoms[6]. The progression of CLL is staged using systems such as Rai and Binet[6]. The Rai system consists of 3 stages: low risk (stage 0), intermediate risk (stages I and II), and high risk (stages III and IV)[6,7]. Median survival for CLL can reach 12.5 years or more for low-risk patients and is about 1.5 years for high-risk patients[8].

A number of treatment options are available to patients with CLL, depending on their stage, age, and health. Treatment options include chemotherapy, targeted therapy, surgery, radiation therapy, stem-cell transplantation, and supportive therapy[9].

Fludarabine, a first-line treatment option for CLL patients, is a purine nucleoside analogue, that, when combined with rituximab, a monoclonal antibody, has been

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shown to increase both overall and complete response rates[10]. Combination therapies such as fludarabine–cyclophosphamide–rituximab have been shown to be effective as first-line treatment for young, fit patients with CLL and are currently considered to be standard therapy[11–13], and yet no national guidelines for the treatment of CLL have been created in Canada. Cancer Care Ontario provides specific guidelines on the use of fludarabine-based treatments and the combination of such therapies with rituximab for intermediate- and high-risk patients with CLL[14].

Although recent publications[12,13] have recommended fludarabine–rituximab combination therapy as a first-line option, that combination is most appropriate for young, fit patients. To avoid the potential adverse events (AEs) associated with fludarabine[15–17], older and less-fit CLL patients are treated with chlorambucil-based treatments. The high cost of rituximab might also influence the use of combination therapy in such patients[18].

In Canada, cost-effectiveness analyses are an important component of the assessment process that leads to a drug being funded on provincial drug formularies. Medical resource utilization and costing data are important inputs. However, those factors have not been well quantified in CLL. Thus, the objective of the present study was to collect medical resource utilization data and costs in Ontario for the management of patients with relapsed or refractory CLL (stratified by Rai staging) who have undergone at least 1 prior treatment course.

METHODS

This retrospective longitudinal cohort study, conducted by chart review, analyzed anonymized patient records from two cancer centres in Ontario: the Odette Cancer Centre at Sunnybrook Health Sciences Centre in Toronto, and the Juravinski Cancer Centre at the Hamilton Health Sciences Centre in Hamilton.

A convenience sample of 90 study participants was proposed, and the clinician at each cancer centre was responsible for generating a patient list based on the inclusion criteria. Between the two sites, 20% of patients were considered ineligible because of another primary cancer, a diagnosis of CLL outside the proposed study time frame, or unavailability of treatment information. If a site had more eligible patients than its target number, patients were randomly selected using a random number generator program.

Patients were eligible for the study if they met all the inclusion criteria:

- Age 18 years or older
- Confirmed diagnosis of CLL between January 2002 and January 2012 (variable follow-up time allowed)
- CLL as the primary cancer
- Disease that was relapsed (progressed after remission based on physician notes) or refractory to treatment (physician indicated no response)
- Receipt of at least 1 treatment
- Complete treatment data available
- Lack of patient comorbidities that could affect overall medical resource utilization (for example, dementia, stroke, multiple sclerosis).

The data collected from patient medical records included demographic and clinical information including age, sex, disease stage, CLL treatments, supportive medications, tests and procedures, specialist visits, and AEs that resulted in hospitalizations and emergency room visits.

Unit costs were derived from a number of sources, including federal and provincial schedules[19–23] and wholesaler catalogues (McKesson, https://www.mckessonspecialty health.com/purchasing-efficiency/product-catalog). The average numbers of resources used were multiplied by unit costs to obtain the cost per resource. All costs are presented in 2014 Canadian dollars unless otherwise specified, in which the stated cost has been inflated using the Bank of Canada Inflation Calculator (http://www.bankofcanada.ca/rates/related/inflation-calculator). Descriptive statistics were used to characterize the demographic, medical resource utilization, and costing data.

RESULTS

Table I shows that the study cohort (n = 86) consisted predominantly of men, and the mean age in the group was 65.1 years. At diagnosis, 22.1% of patients had stage I disease. Reported mortality was 26.7%. Furthermore, for patients who reported employment status, 27.9% were retired.

Table II presents follow-up and total cost data for the patients overall and by stage. Overall, mean follow-up was 4.7 years (median: 4.5 years; range: 0.2–12.0 years), and total mean cost per patient was $25,736 (median: $19,619; range: $1,010–$181,860).

Table III shows that a total of 183 CLL treatments were administered in the cohort, with fludarabine having the highest utilization (70 treatments). Patients receiving chlorambucil (61 treatments) stayed on treatment longer and had a higher mean cost per patient ($18,738).

DISCUSSION AND CONCLUSIONS

The present study is the first to evaluate standard medical resource utilization and associated costs in the management of patients with relapsed and refractory CLL in Canada. A cohort of 86 individuals from Ontario, diagnosed with CLL from January 2002 to 2012, was evaluated. The median follow-up time was 4.5 years, and the mean cost per patient was $25,736, with CLL treatments accounting for more than half that cost. As first-line treatment, a chlorambucil-based regimen was prescribed for 48.8% of the patients; 44.2% received a fludarabine-based regimen in the first line. For second-line treatment, fludarabine-based regimens were the most prescribed (38.9%), followed by chlorambucil-based regimens (22.2%). The stage IV subgroup had the highest mean cost per patient because the average cost of managing AEs was approximately $22,000 [a small number of patients ($n < 5$) who experienced multiple AEs accounted for the high management costs].

The mean time to relapse or refractory disease was 1 year (365.6 days). Some chemotherapies were repeated in second-line treatment because sufficient time had passed that the same therapy could be expected to be efficacious. Chlorambucil was repeated in older patients who would not be able to tolerate stronger treatment.

TABLE I Demographics and clinical information

Characteristic	Value
Patients (*n*)	86
Age at diagnosis (years)	
Mean	65.1±12.0
Median	66
Range	37–93
Sex [*n* (%)]	
Men	59 (68.6)
Women	27 (31.4)
Follow-up (years)	
Mean	4.7±2.4
Median	4.6
Range	0.2–12.0
Mortality [*n* (%)]	23 (26.7)
Rai stage [*n* (%)]	
0	10 (11.6)
I	19 (22.1)
II	16 (18.6)
III	11 (12.8)
IV	15 (17.4)
Not reported	15 (17.4)
Comorbidities[a] [*n* (%)]	
Hypertension	30 (44.7)
Diabetes	17 (25.4)
Hyperlipidemia	15 (22.4)
Osteoarthritis or osteoporosis	3 (4.5)
COPD	2 (3.0)
Employment status at diagnosis[b] [*n* (%)]	
Retired	24 (27.9)
Employed full-time	20 (23.3)
Employed part-time	3 (3.5)
Disability	2 (2.3)
Unemployed	2 (2.3)

[a] Reported by 39 patients.
[b] Reported by 51 patients.
COPD = chronic obstructive pulmonary disease.

Of interest were the lower attributable mean and total costs for the stage III subgroup compared with the stages I and II subgroups. That finding is explained by the fact that 4 patients with stage III disease received clinical trial treatments and therefore did not incur treatment costs. Excluding those patients would yield a higher cost for the subgroup.

Limitations of our study include the small sample size representing all patients with CLL, the generalizability of results from two centres to all of Ontario, and the comprehensiveness of the data extracted, which depended on the comprehensiveness of the medical records. Disease stage was unknown for 15 of the patients. Knowing the stage for those patients, allowing them to be categorized for the analysis, would have resulted in a more accurate estimate of costs per stage.

Another study limitation was the difference between the mean and median costs of the resources; the small number of patients with extremely high costs skewed those data. Also, the wide range of costs for specific CLL treatments were a reflection of how each drug was prescribed by the physician.

For this Canadian CLL cohort, medical resource utilization and costs were determined to be $2.2 million in total. The CLL treatments accounted for about half that cost, and the cost generally increased with disease stage. Fludarabine- and chlorambucil-based regimens remained the preferred treatment options for these patients.

The treatment landscape for CLL in Canada continues to evolve. Our study includes treatment information up to 2012, but other agents for the treatment of CLL have been approved in Canada since that time. Further studies will be needed to evaluate the costs associated with the newer therapies.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SH and SJS declare consultancies through the HOPE Research Centre, a group that consults to the pharmaceutical industry. BK and CT are employees of Janssen Inc. NM declares educational programs, unrestricted funding, and consultancies through the HOPE Research Centre, a group that consults to the pharmaceutical industry and with which she was affiliated at the time of study; however, that affiliation ended in 2015 and before publication of the study.

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TABLE II Mean and total costs by disease stage at diagnosis

Variable	Stage						
	All (*n*=86)	0 (*n*=10)	I (*n*=19)	II (*n*=16)	III (*n*=11)	IV (*n*=15)	Unknown (*n*=15)
Follow-up (years)							
Mean	4.7±2.4	5.7±2.5	4.3±1.8	4.9±3.0	5.4±2.6	4.8±2.7	3.6±1.9
Median	4.5	5.0	3.9	4.5	5.9	4.0	3.8
Range	0.2–12.0	2.9–11.9	2.1–8.2	0.4–12.0	1.9–8.9	0.2–10.5	0.2–5.9
Overall cost per patient ($)							
Mean	25,736±25,733	25,752±29,089	19,203±26,863	27,481±29,540	17,606±19,134	48,025±64,932	15,810±19,660
Median	19,619	24,408	14,989	28,909	12,511	38,587	7,179
Range	1,016–181,860	4,732–56,647	1,230–60,899	1,016–70,846	1,016–55,666	11,912–181,860	459–64,303
Costs by resource ($)							
CLL treatments							
Total	1,237,424	160,175	219,473	307,229	123,866	326,296	100,385
Mean	14,389±15,005	16,018±12,690	11,551±15,346	19,202±17,576	11,261±12,957	21,753±17,185	6,692±6,679
Supportive medications							
Total	20,167	3,720	3,844	3,617	1,992	6,144	851
Mean	280±463	372±676	202±366	226±234	181±187	410±715	57±83
Tests and procedures							
Total	81,420	9,035	20,625	18,184	9,209	18,375	5,992
Mean	947±687	903±459	1,086±805	1,137±720	837±674	1,225±693	399±246
Specialist visits							
Total	191,099	25,708	40,750	38,285	22,257	39,742	24,358
Mean	2,222±1,252	2,571±1,514	2,145±934	2,393±1,453	2,023±1,218	2,649±1,362	1,624±1,006
Adverse events							
Total	683,156	58,882	80,168	72,374	36,342	329,824	105,565
Mean	11,986±25,341	5,888±13,750	4,219±9,412	4,523±9,558	3,304±4,099	21,988±44,977	7,038±11,546
Aggregate total cost ($)	2,213,266	257,520	364,860	439,690	193,666	720,381	237,150

CLL = chronic lymphocytic leukemia.

TABLE III Summary of overall resource use and costs

Resource	Resource (*n*)			Cost per patient ($)		Total cost of resource ($)
	Users	Used	Mean per user	Median	Range	
CLL treatments	86	183	2.1	9,272	39–61,430	1,237,424
Fludarabine-based	38	70	2.0	5,770	39–52,331	435,849
Chlorambucil-based	42	61	2.2	15,783	87–61,430	786,986
Other treatments	6	52	3.3	1,423	59–6,390	14,589
Supportive medications	72	418	5.8	168	1–2,685	20,167
Tests and procedures	86	3159	36.7	812	41–2,830	81,420
Specialist visits	86	2312	26.9	80	317–6,385	191,099
Adverse events	57	106	1.9	4,128	80–168,352	683,156

CLL = chronic lymphocytic leukemia.

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