Cost-effectiveness analysis of different combination therapies for the treatment of chronic lymphocytic leukaemia in India

Prerika Nehra,[a] Akashdeep Singh Chauhan,[a] Pankaj Malhotra,[b,**] Lalit Kumar,[c] Ashish Singh,[d] Nidhi Gupta,[e] Nikita Mehra,[h] Anisha Mathew,[c] Amal Chandra Kataki,[f] Sudeep Gupta,[g] and Shankar Prinja[a,*]

[a]Department of Community Medicine and School of Public Health, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[b]Department of Clinical Haematology and Medical Oncology, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[c]Department of Medical Oncology, All India Institute of Medical Sciences (AIIMS), New Delhi, India
[d]Department of Medical Oncology, Christian Medical College, Vellore, Tamil Nadu, India
[e]Department of Radiation Oncology, Government Medical College and Hospital, Chandigarh, India
[f]Department of Gynaecologic Oncology, Dr. B. Booroah Cancer Institute, Guwahati, Assam, India
[g]Department of Medical Oncology, Tata Memorial Centre, Mumbai, Maharashtra, India
[h]Department of Medical Oncology, Adyar Cancer Institute, Chennai, Tamil Nadu, India

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Summary

Background Over the years, there has been introduction of newer drugs, like bendamustine and ibrutinib, for the management of chronic lymphocytic leukaemia (CLL). Though these drugs lead to better survival, they are also associated with higher cost. The existing evidence on cost effectiveness of these drugs is from high-income countries, which has limited generalisability for low-income and middle-income counties. Therefore, the present study was undertaken to assess the cost-effectiveness of three therapeutic regimens, chlorambucil plus prednisolone (CP), bendamustine plus rituximab (BR) and ibrutinib for CLL treatment in India.

Methods A Markov model was developed for estimating lifetime costs and consequences in a hypothetical cohort of 1000 CLL patients following treatment with different therapeutic regimens. The analysis was performed based on a limited societal perspective, 3% discount rate and lifetime horizon. The clinical effectiveness of each regime in the form of progression-free survival and occurrence of adverse events were assessed from various randomised controlled trials. A structured comprehensive review of literature was undertaken for the identification of relevant trials. The data on utility values and out of pocket expenditure was obtained from primary data collected from 242 CLL patients across six large cancer hospitals in India.

Findings As compared to the most affordable regimen comprising of CP as first-line followed by BR as second-line therapy, none of the other therapeutic regimens were cost-effective at one time per capita gross-domestic product of India. However, if the current price of either combination of BR and ibrutinib or even ibrutinib alone could be reduced by more than 80%, regimen comprising of BR as first-line therapy followed by second-line ibrutinib would become cost-effective.

Interpretation At the current market prices, regimen comprising of CP as first-line followed by BR as second-line therapy is the most cost-effective strategy for CLL treatment in India.

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Keywords: Cost effectiveness; Leukaemia; Chemotherapy; Economic evaluation

Introduction

Chronic lymphocytic leukaemia (CLL) in India accounts for around 7673 new cases and approximately 6195 deaths annually.[1] Though the incidence of CLL, with 4.1 cases per million in India, is lower than in western regions of the world, the CLL patients in India are

*Corresponding author.
**Corresponding author.
E-mail addresses: shankarprinja@gmail.com (S. Prinja), malhotrapankaj@hotmail.com (P. Malhotra).

Research in context

Evidence before this study

We reviewed the existing literature related to full economic evaluations and published till December 31, 2021. PubMed was searched using the following search string: ((((((((((cost effectiveness analysis*) OR (cost utility analysis*)) OR (cost benefit analysis*)) OR (economic evaluation)) OR (pharmacoeconomic analysis*)) OR (pharmacoeconomic evaluation)) OR (health technology assessment)) OR (HTA)) OR (cost-benefit analysis [MeSH Terms]))))) AND (((((chronic lymphocytic leukaemia) OR (chronic leukaemia)) OR (CLL)) OR (B cell leukaemia)) OR (B cell chronic lymphocytic leukaemia)). The initial search yielded 437 results, of which 420 were eliminated based on the screening of title and/or abstract. The remaining 17 papers were reviewed in detail, based on which six records which assessed the cost-effectiveness of various anti-chronic lymphocytic leukaemia (anti-CLL) drugs were selected. The search revealed that all the existing studies on the cost effectiveness of anti-CLL drugs were all conducted in the context of high-income countries. Furthermore, none of the studies directly compared the three drugs in question of our study, i.e., chlorambucil, bendamustine and ibrutinib. In view of limited generalisability of the evidence from the high-income countries, the present study was undertaken to assess the cost-effectiveness of three treatment regimes—i.e., chlorambucil plus prednisolone (CP), bendamustine plus rituximab (BR), and ibrutinib for the treatment of CLL in India.

Added value of this study

The present study is first of its kind that has comprehensively analysed and compared not only the first-line anti-CLL drugs, but also assessed the cost-effectiveness of various combinations of first-line and second-line therapies. We compared and modelled four treatment strategies. The first arm 'A' comprised CP as first-line therapy and BR as second-line therapy. Similarly, the second arm 'B' constituted CP as first-line therapy and ibrutinib as second-line therapy. The third arm 'C' consisted of BR as first-line therapy and ibrutinib as second-line therapy. Lastly, in the fourth arm 'D', ibrutinib was considered first-line therapy followed by BR as the second-line therapy. The study shows that at current prices the regimes comprising of first-line bendamustine or ibrutinib are not cost-effective and the standard treatment with first-line chlorambucil based therapy is cost-effective in the Indian context. However, if the prices of both BR and ibrutinib are reduced by more than 80%, strategy of BR as first-line and ibrutinib as second-line therapy starts to become cost-effective. The study also points to the fact that delaying ibrutinib until later lines of therapy may be a reasonable strategy to limit healthcare costs without compromising health outcomes.

Implications of all the available evidence

The decisions on the reimbursement of new drugs under insurance programs are heavily dependent on evidence for cost-effectiveness. Moreover, evidence on value-based price is important for any price negotiations by procurement agencies or price-setting by regulatory agencies. The present study provides robust evidence on how much should be the reduction in the existing market prices of newer drugs i.e., bendamustine and ibrutinib, at which they are cost effective and could potentially be considered for reimbursement under India's national health insurance scheme of Ayushman Bharat Pradhan Mantri Jan Arogya Yojana (AB PM-JAY).

generally diagnosed at younger age with poor performance status and have high morbidity burden.[2] The median age at diagnosis of CLL patients in India has been reported as 61 years which is almost a decade younger than the median age of 70 years in western countries.[3,4] Furthermore, the Eastern Cooperative Oncology Group (ECOG) performance status scale of ≥ 2 has been reported in 24.7% of patients in India but in only 3–8% of patients in western countries.[4–6] In terms of disease presentation, around 32% of the patients with CLL in India are diagnosed in Rai stage 0 or stage I, 25.4% in stage II and the remaining one-third in stage III or IV.[4] While patients in stages 0, I and II are mostly kept on observation and treatment is initiated when there is progression, those in stage III and IV are immediately put on radical treatment.[4] General considerations for treatment are symptomatic disease, performance status, age and high risk cytogenetics.[2,7]

Chlorambucil, a drug no longer in practice in high-income countries is still commonly prescribed in India mainly for financial reasons as it is more affordable when compared to newer drugs like bendamustine or Ibrutinib.[4,8] Affordability and availability of finances with the households is an important criterion in India while finalizing the treatment regimen in addition to performance status and prognostic factors. Thus, only those households, which can afford or with some pre-payment mechanisms (i.e., health insurance) are able to avail the treatment according to international guidelines.[9] However, the treatment gets delayed or modified if there is limitation in finances.[9] A study by Tejaswi and colleagues provided a real-world evidence and a glimpse of treatment to CLL patients in India.[4]

Globally, chlorambucil has shown decent clinical effectiveness in the management of CLL and was also used to be the first-line treatment before the introduction of bendamustine and ibrutinib, especially for elderly patients and patients with co-morbidities.[10–12] As compared to chlorambucil, both bendamustine [Median progression-free survival (PFS); 21.6 months versus 8.3 months; $p < 0.0001$] and ibrutinib (70% versus 12% at 5 years) have significantly high PFS.[13,14] Also, ibrutinib has

relatively higher PFS (87% versus 74% at 2 years; $p < 0.001$) than bendamustine.[5] Patients treated with chlorambucil, had shown a lower incidence of neutropenia (13.9%) and thrombocytopenia (20.5%) compared to bendamustine (27.3% with neutropenia and 24.8% with thrombocytopenia).[13] While, administration of ibrutinib leads to lower incidence of neutropenia (10%) and thrombocytopenia (2%), it is associated with higher rates of pneumonia (4%), lower infections (10%) and atrial fibrillation (3%).[5,14]

Though the newer drug regimens lead to better survival,[4,5,13,15] they are also associated with higher cost. A study from India showed that the six-month expenditure for CLL treatment with ibrutinib (12,000 US$) and bendamustine (2300 US$) was around 200 times and 40 times higher than chlorambucil-based regimen (60 US$), respectively.[4] With continuous new advancements in drug technology for CLL treatment and with limited budgets in the health sector, it becomes crucial to assess the cost-effectiveness of newer interventions along with their health benefits. However, there is no available evidence on the cost-effectiveness of anti-CLL from India or even the South-East Asia Region (SEAR). All the existing literature on the cost-effectiveness of these drugs has been reported from the context of developed nations.[12,16–23] Moreover, none of these economic evaluations have directly compared the three drugs in question, i.e., chlorambucil, bendamustine and ibrutinib.

Recently, India's National Pharmaceutical Pricing Authority (NPPA) has undertaken a price regulation of about 42 anticancer drugs including various anti-CLL drugs. Considering the same, the Health Technology Assessment India (HTAIn) commissioned the present study to assess the cost-effectiveness and value-based price of these drugs. In view of limited generalisability of the evidence from the high-income countries, the present study was undertaken to assess the cost-effectiveness of three treatment regimes: chlorambucil plus prednisolone (CP), bendamustine plus rituximab (BR), and ibrutinib for the treatment of CLL in India.

Methods

Model overview

A Markov model was developed to estimate costs and health outcomes in a hypothetical cohort of 1000 CLL patients following treatment with different therapeutic regimens. The analysis was based on a limited societal perspective which included health system costs and out-of-pocket (OOP) expenditures.[24] We excluded the indirect cost both due to productivity losses and premature mortality. A lifetime horizon with a discount rate of 3% was used as per India's HTA guidelines.[24] Health outcomes were assessed in term of life years (LY) and quality-adjusted life years (QALY).

The Markov model (Fig. 1), representing various health states of CLL patients following diagnosis and undertaking first-line of treatment for CLL, was developed. During the duration of treatment, patients were presumed to develop severe adverse events (AE-1) or mild side-effects.[4,5,13,15] Those patients with severe AE-1 were assumed to discontinue the treatment and either receive the second-line therapy, face a probability of dying (cause specific or all-cause mortality), develop progression, or move back to receive the initial first-line therapy following treatment of AE-1.[4,5,13,15] Mild side effects were assumed to be pharmacologically managed alongside the treatment. Based on the clinical response following first-line treatment, patients were assumed to be either in stable/disease-free, defined as the progression-free state (PFS-1), or could develop progressive disease (PD-1). Those patients in the PFS-1 state further faced a probability of developing the progressive disease (PD-1) or dying from the all-cause mortality. Last, patients in PD-1 state were either assumed to die because of the disease-specific/all-cause mortality or were assumed to receive the second-line therapeutic regimen. As per clinical guidelines, the patients with progressive disease are not eligible to receive treatment.[7] So as per the expert opinion, 50% of patients who developed PD-1 were assumed to wait for six months, and the remaining 50% wait for 12 months before receiving the second-line of treatment.[4,7]

Patients on second-line therapy had a similar clinical course, as followed during the first-line treatment. However, we did not assume any third-line therapy for patients with adverse events (AE-2) and progressive disease (PD-2). Specifically, the treatment of patients with AE-2 was discontinued, and these patients were assumed to either progress to PD-2, die (from cause specific or all-cause mortality) or move back to receive the second-line therapy itself following treatment of AE-2. Lastly, patients in PD-2 stage were directly assumed to die due to disease specific or all-cause mortality. We included grade 3 or higher infection with pneumonia and atrial fibrillation as severe adverse events. Furthermore, neutropenia and thrombocytopenia were modelled as mild side effects. Based on the standard treatment guidelines for duration of treatment with chlorambucil and bendamustine, the cycle length was assumed to be of six months.[7] The model was assumed to start at 60 years of age, which is the mean age at diagnosis with CLL in India.[4]

Treatment arms

Based on clinical consultation, we modelled four treatment arms as the base case. The first arm 'A' comprised CP as first-line therapy and BR as second-line therapy. Similarly, the second arm 'B' constituted CP as first-line therapy and ibrutinib as second-line therapy. The third arm 'C' consisted of BR as first-line therapy and ibrutinib as second-line therapy. Lastly, in the fourth arm 'D', ibrutinib was considered first-line therapy followed by BR as the second-line therapy.

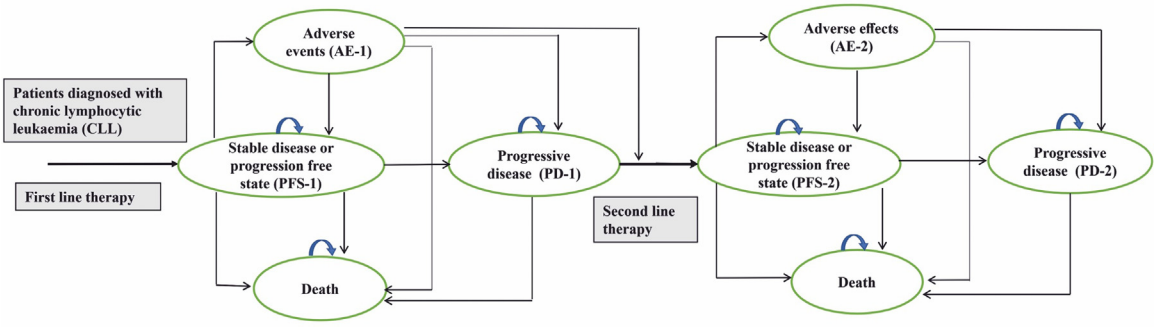

Fig. 1: **Markov model.**

In addition to the four primary treatment arms, three scenario analyses were undertaken. Under these scenarios, CP (treatment arm 'E'), BR (treatment arm 'F') and ibrutinib (treatment arm 'G') were each given as first-line therapy with no additional second-line treatment. The primary purpose of the scenario analysis was to directly compare and assess the cost-effectiveness of the three drugs in question, while excluding the impact of the second-line therapy. Dosage of chlorambucil and prednisolone was taken as 10 mg/m^2 and of 60 mg/m^2 respectively for five days in a 28-day cycle, for 6 cycles.[4] The dose for bendamustine was estimated as 90 mg/m^2 on day 1 and 2, along with rituximab (375 mg/m^2 on day 1) in a 28-day cycle, for 6 cycles.[4] Ibrutinib was administered at a dose of 420 mg daily.[5,15] Dosage was considered the same for the first and second-line of treatment.

Clinical effectiveness and transition probabilities

The data on progression and occurrence of adverse events with administration of each drug (both for first-line and second line) was obtained from various randomised controlled trials (RCTs) as shown in Table 1. A structured comprehensive review of literature was undertaken in the PubMed with specific key words for the identification of relevant RCTs comparing effectiveness and safety between chlorambucil, bendamustine and ibrutinib. First, all the published RCTs globally were searched that had either compared all the three drugs or a minimum of two drugs among the three drugs in question. Second, as there were no published RCT reported from India, search strategy was expanded to look for observational studies comparing the effectiveness and safety of these three drugs from India. Studies published in English language till December 31, 2021 and those including previously untreated CLL patients with a performance status of between 0 and 2 were considered. Later, expert group meetings with senior oncologists from two large public tertiary care hospitals of India were conducted for identification of the relevant studies for inclusion in the present analysis. In case where more than one RCT reported results on the same treatment-outcome effect, no averaging was done, and the decision to consider which specific study was solely based on the expert opinion of the clinicians, that considered various criteria like sample size, follow-up period, baseline characteristics of patients, etc.

The probability of progression was calculated using the PFS survival curves reported in these trials.[5,6,25,26] Estimation of survival beyond the follow up period, necessitates the use of extrapolation beyond the trial period. Hence, the PFS curves from each trial were extrapolated using standard methods.[29] Firstly, the individual patient-level data was created using an online tool from the published PFS curves.[30] This patient-level data was then extrapolated using different parametric models (Gompertz, Weibul, Log-logistic, etc.) in Stata.[29,30] The preferred model was selected using the Akaike's Information Criterion (AIC) and Bayesian Information Criterion (BIC), and on the visual comparison of published Kaplan–Meier and fitted survival curves.[29]

Table 1 shows the results of fitting parametric survival curves of the time to progression (TTP). Fig. 2 shows the empirical and fitted survival curves for TTP for each of first-line and second-line therapy. The time dependent six-monthly transition probabilities of moving from PFS-1 to PD-1 were derived for all first-line therapies. Data on disease specific mortality was assessed from a study that had reported survival up till 10 years following treatment initiation. Because around 80% of the CLL patients died at 10 years, parametric survival functions were not applied and an actual probability of dying from the published curve was used.

A constant transition probability was used for the post progression i.e., PFS-2 to PD-2 for second-line therapies. Likewise, a constant probability of disease specific mortality was assumed. This approach was justified as the incorporation of time dependent probability of moving from PFS-2 to PD-2 or progressive disease to death would have greatly increased the complexity of the model.

The probability of death from adverse events was calculated using the data from Institute for health metrics and evaluation (IHME), Global burden of Disease Study.[1] The data on the percentage of patients discontinuing the treatment following adverse events was

Parameter	Estimate	Range/SE	Source
PFS for CP as first-line therapy	Weibull; λ = 0.016834 γ = 0.3373993	λ = 0.004638 γ = 0.064348	Hillmen et al.[6]
PFS for BR as first-line therapy	Gompertz; λ = 0.008776 γ = 0.0259679	λ = 0.002134 γ = 0.009710	Woyach et al.[5]
PFS for ibrutinib as first-line therapy	Exponential; λ = 0.0057715	λ = 0.001004	Woyach et al.[5]
PFS for BR as second-line therapy	Log-logistic; λ = 3.021232 γ = −0.6195551	λ = 0.224552 γ = 0.2577661	Ghia et al.[25]
PFS for ibrutinib as second-line therapy	Exponential; λ = 0.0176984	λ = 0.003539	Huang et al.[26]
Incidence of severe adverse events with CP as first line therapy	27	2.755	Hillmen et al.[6]
Incidence of adverse events with BR as first-line therapy	31	3.163	Woyach et al.[5]
Incidence of adverse events with ibrutinib as first-line therapy	54	5.510	Woyach et al.[5]
Incidence of adverse events with BR as 2nd line therapy	5	0.510	Ghia et al.[25]
Incidence of adverse events with ibrutinib as second-line therapy	23	2.346	Huang et al.[26]
Proportion of patients receiving 2nd line therapy following adverse events with CP as first-line therapy	0.099	0.010	Hillmen et al.[6]
Proportion of patients receiving 2nd line therapy following adverse events with BR as first line therapy	0.17	0.017	Ghia et al.[25]
Proportion of patients receiving second-line therapy following adverse events with ibrutinib as first line therapy	0.024726	0.002523	Huang et al.[26]
Annual disease specific mortality rate with CLL	0.148913	0.015195	Gogia et al.[8]
Age-specific all-cause annual mortality rates			
60–65 years	0.0907	0.009	SRS life tables
65–70 years	0.01346	0.013	
70–75 years	0.2006	0.020	
75–80 years	0.2969	0.029	
80–85 years	0.4503	0.045	
Case fatality rate for pneumonia	0.1265	0.012	GBD, 2019
Case fatality rate for atrial fibrillation	0.003	0.0004	GBD, 2019
Health state utility values			
Progression free state (PFS-1) following first-line therapy	0.806	0.082	[b]
Progressive disease (PD-1) following first-line therapy	0.64873	0.066	[b]
Progression free state (PFS-2) following second-line therapy	0.69788	0.071	[b]
Progressive disease (PD-2) following second-line therapy	0.57993	0.059	[b]
Stable disease plus atrial fibrillation following first-line therapy[a]	0.65286	0.066	Sullivan et al.[27]
Stable disease plus pneumonia following first-line therapy[a]	0.332072	0.033	Galante et al.[28]
Stable disease plus atrial fibrillation following second-line therapy[a]	0.565283	0.057	Sullivan et al.[27]
Stable disease plus pneumonia following second-line therapy	0.287527	0.029	Galante et al.[28]

CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; PD: Progressive disease; PFS: Progression free state; CLL: Chronic Lymphocytic Leukaemia. [a]The utility values were calculated separately for adverse event atrial fibrillation and pneumonia which along with utility values of CLL, using multiplicative methods. [b]Obtained based on the primary data collection, as part of the Cancer Database for Cost and Quality of Life (CaDCQoL).

Table 1: **Model input parameters.**

used to calculate the probability from AE-1 to PFS 2 (Table 1).[5,6,25,26] The CLL specific mortality was specifically assessed from an Indian study, that had reported survival rate following first-line treatment of CLL.[8] All-cause mortality rates were assessed from Sample Registration System (SRS) Life Tables of India-2014-2018.[31]

Utility scores

Utility values for progression-free and post-progression health states were obtained based on the primary data collection from 242 CLL patients from six large cancer hospitals across India, as part of the Cancer Database for Cost and Quality of Life (CaDCQoL).[32] The patients were administered the EQ-5D-5L tool, and India specific tariff values were used for estimating the utility score for the health states (Table 1). The utility value for adverse events i.e., atrial fibrillation and pneumonia, was assessed from the published literature.[27,28,33]

Costs

As mentioned above, we included both the health systems costs and patient-level OOP expenditure incurred

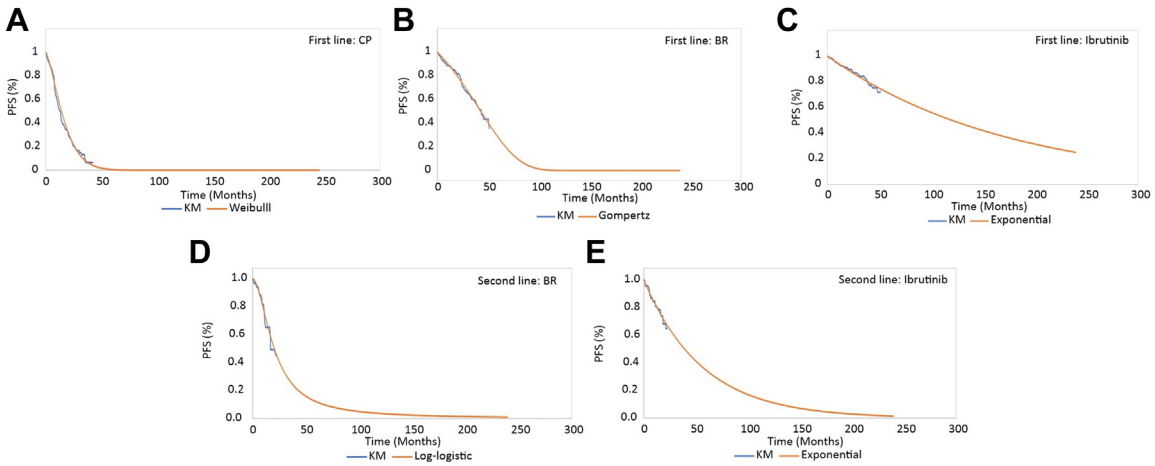

Fig. 2: **Comparison of empirical and fitted progression free survival curves.** CP: Chlorambucil plus prednisolone, BR: Bendamustine plus rituximab, KM: Kaplan–Meier, PFS: Progression-free survival.

during the length of CLL treatment. Health systems costs accounted for outpatient consultation, diagnostic tests, day-care (Table 2). Further, OOP expenditure included the direct non-medical expenses incurred on travel boarding/lodging, food, and user fees during the treatment (Table 2). The unit health system cost of day-care was assessed from a previous costing study from India.[34] The unit cost of outpatient consultation and diagnostic tests were assessed from the reimbursement rates of India's national social health insurance, i.e., the Central Government Health Scheme (CGHS).[35] Due to a lack of information on the cost of

Parameter	Estimate	95% Confidence interval	Source
Health system cost (US$)			
Outpatient consultation (per visit)	2.02	1.23–2.80	35
Day-care (per visit)	14.00	8.436–19.56	34
CBC (per test)	1.88	1.15–2.60	35
Flow-cytometry (per test)	32.34	19.03–45.64	44
Serum chemistry panel (per test)	19.81	11.91–27.70	35
Chest X-ray (per test)	0.80	0.48–1.11	35
IGVH mutational status (per test)	101.17	60.75–141.58	36
Serum beta-2 microglobulin (per test)	1.40	0.85–1.94	35
Abdominal ultrasound (per test)	4.35	2.60–6.09	35
FISH test (per test)	6.74	4.05–9.42	35
Cost of peripheral smear (per test)	0.60	0.36–0.83	35
Price of drugs (₹)			
Ibrutinib (per mg)	1.714	1.03–2.39	38
Bendamustine (per mg)	18.11	10.87–25.34	39
Rituximab (per mg)	52.99	29.00–76.97	40
Chlorambucil (per mg)	16	9.60–22.39	41
Prednisolone (per mg)	0.082	0.05–0.11	42
Out-of-pocket expenditure (Monthly; US$)			
Direct non-medical expenses	34.31	20.59–48.02	Primary data
Cost of managing adverse events (US$)			
Neutropenia	109.98	66.03–153.92	Normative costing
Thrombocytopenia	2.91	1.75–4.06	Normative costing
Atrial fibrillation	24.28	14.58–33.97	37
Pneumonia	24.28	14.58–33.97	37

₹: Indian Rupees; US$: United States Dollar; CBC: Complete Blood Count; IGVH: Immunoglobin heavy chain gene; FISH: Fluorescence in situ hybridization.

Table 2: **Costs parameters.**

immunoglobin heavy chain gene (IGVH) mutational tests, markets prices of the same were used.[36] The data on OOP expenditure were based on analysis of primary data being collected as part of CaDCQoL database.[32] The cost for treating neutropenia and thrombocytopenia was calculated using normative costing. The cost of treatment for atrial fibrillation and pneumonia was assessed using the provider payment rates of Ayushman Bharat Pradhan Mantri Jan ArogyaYojana (AB PM-JAY).[37] Market prices of ibrutinib, bendamustine, chlorambucil, and other drugs (used in the analysis) were used in the present analysis.[38–42] The cost of the drugs was calculated based on the quantity of drug required as per the average weight and height of Indian population from the report of expert group on nutrient requirements for Indians, 2020.[43]

The information on the type and quantity of various health services (outpatient consultation, day-care, etc.), including diagnostic tests undertaken before and during the CLL treatment, was assessed using the standard treatment guidelines, international workshop on chronic lymphocytic leukaemia (iwCLL) guidelines, and the clinician's expert opinion.[7] The quantities were then multiplied by the unit cost of respective health services to estimate the total cost of CLL treatment. Finally, the total cost comprised of initial baseline cost incurred during the diagnosis process (includes diagnostics and outpatient consultations), delivery of therapeutic regimen (consisting of the price of drugs and day-care cost), management complications and adverse effects, and follow-up sessions. All the cost estimates belong to the year 2020. Cost estimates are presented in United States Dollar (US$). A conversion rate for the year 2020 of 1 US$ = ₹74.13, as reported by the World Bank, was used.

Sensitivity analysis

A multivariable probabilistic sensitivity analysis (PSA) was undertaken for estimating the effect of joint parameter uncertainty. Under PSA, all cost parameters were assigned gamma distribution, while utility values and probabilities/proportions were assigned beta distribution. A 40% and 20% variation on either side of the base value was used for cost and clinical parameters, respectively. Based on 1000 Monte Carlo simulations, median value of incremental cost-effectiveness ratio (ICER) along with 2.5th and 97.5th percentile was computed and reported. GDP per capita of US$ 1965 for India in year 2020 was considered as the threshold of cost effectiveness.

A threshold analysis was undertaken to understand the effect of varying the prices of drugs on the results. Prices of BR and ibrutininb were decreased by 20%, 50%, 80% and 90% and the respective ICERs were compared.

Dominance analysis

Dominance analysis was performed to compare the cost-effectiveness of treatment arms. When a treatment option is less costly and more effective, it 'dominates' the comparators (referred to as 'dominated'). Further, when a linear combination of two strategies produces a greater effect at a lower cost than some other strategy, then this combination of former two strategies 'extendedly dominates' the latter strategy. The dominance analysis was undertaken to eliminate those strategies that get 'dominated' or 'extendedly dominated', and finally to identify the dominant strategies. Dominance analysis was performed for base case treatment arms of A, B, C and D and separately for scenarios E, F and G. In addition, a separate dominance analysis was performed, each time, when the price of a BR or ibrutinib was varied. This analysis was conducted using R Shiny app and commands for ICER calculator.[45]

Ethical approval

Ethical approval was obtained from the Institutional Ethics Committee of Post Graduate Institute of Medical Education and Research, India, with reference number IEC-03/20202-1565.

Role of the funding source

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Results

The absolute number of LYs and QALYs lived, along with lifetime cost incurred on the treatment of CLL patient following treatment with various treatment arms included in the base case and scenario analysis has been mentioned in Table 3. Compared to the treatment arm A, a CLL patient gained 0.93 (0.53–1.35) to 6.93 (6.49–7.38) LYs and 0.7 (0.37–1.11) to 5.9 (4.28–7.17) QALYs at an additional cost of 9449 US$ (5496–14,660) to 44,545 US$ (31,404–60,973) following treatment with the other three treatment arms included in the base case analysis (Table 4). This resulted in an incremental cost of 10,522 US$ (5917–18,721), 7151 US$ (4273–11,375), and 6432 US$ (4502–8792) per LY gained with treatment arms B, C and D respectively as compared to arm A. Similarly, ICER, as US$ per QALY gained, came out to be 14,071 US$ (7474–24,983), 4652 US$ (3052–6837), and 7669 US$ (5011–11,701) with treatment arms B, C and D, respectively, as compared to arm A. Furthermore, the resulting ICERs (per QALY gained) were 1149 US$ (440–2095) and 6906 US$ (4497–10,988) when treatment arms C and D were compared against arm B. Lastly, the use of treatment arm D as compared to arm C resulted in an ICER (per QALY gained) of 9948 US$ (6287–16,568). The cost-effectiveness plane (supplement material; Table S1, Fig. S1) showed that all the four treatment arms were non-dominant.

Strategy	First-line regimen	Second-line regimen	Cost per person in US$*	Life years lived per person*	QALYs lived per person*
A	CP	BR	4356 (3517–5441)	5.63 (4.98–6.24)	3.8 (3.22–4.46)
B	CP	Ibrutinib	13,805 (9798–18,997)	6.57 (5.86–7.25)	4.51 (3.81–5.23)
C	BR	Ibrutinib	15,804 (12,090–20,602)	7.3 (6.93–7.72)	6.3 (5.39–7.11)
D	Ibrutinib	Ibrutinib	48,901 (35,419–65,173)	12.57 (12.27–12.87)	9.71 (7.77–11.04)
E	CP	–	1573 (1222–1984)	4.19 (3.57–4.82)	2.94 (2.3–3.62)
F	BR	–	4981 (3924–6324)	6.09 (5.7–6.53)	4.5 (3.72–5.16)
G	Ibrutinib	–	41,342 (29,118–56,493)	11.42 (11.17–11.69)	8.96 (7.12–10.28)

CP: Chlorambucil plus prednisolone; BR: Bendamustine plus rituximab; US$: United States Dollar; QALY: Quality adjusted life years. *Figures in parenthesis indicate 2.5th and 97.5th percentile.

Table 3: **Discounted probabilistic median absolute outcomes of the treatment arms included in the base case and scenario analysis.**

Among the treatment arms included in the scenario analysis, a CLL patient following treatment with arms F and G led to a gain of 1.89 (1.44–2.03) to 7.22 (6.74–7.68) life years and 1.56 (1.06–2.03) to 6.02 (4.41–7.22) QALYs at an additional cost of 3407 US$ (2486–4666) and 39,768 US$ (27,510–54,979), respectively, compared to arm E (Table 5). The resultant ICER (US$ per LY gained) were computed to be 1824 US$ (1240–2653) and 5509 US$ (3806–7557) with the treatment arm F and G as compared to arm E. Similarly, incremental cost per QALY gained following treatment with arm F and G were estimated to be 2237 US$ (1452–3401) and 6711 US$ (4423–10,245) compared to arm E. All the three treatment arms were non-dominant as shown in supplement material: Table S2 and Fig. S2.

Threshold analysis

If the current price of either combination of BR & ibrutinib or even ibrutinib alone is reduced by more than 80%, regimen comprising of BR as first-line therapy followed by second-line ibrutinib, starts to become cost effective (Fig. 3; Supplementary material: Tables S3–S12; Figs. S3–S12). Further, price threshold analysis of single line treatment regimens shows that with decrease in the price of BR by 20% strategy F becomes cost effective. Similarly, by decreasing the price of ibrutinib by more than 80% strategy G starts to become cost-effective (Supplementary material: Tables S13–S19; Figs. S13–S20).

Discussion

With no previous economic evaluation assessing the cost-effectiveness of anti-CLL drugs, especially from low and middle-income countries (LMIC) in the SEAR region, the present study was undertaken to determine the cost-effectiveness of various therapeutic regimens in treatment-naive patients of CLL in India. The results show that newer treatments regimes comprising of first-line bendamustine or ibrutinib are not cost-effective at

Incremental outcomes*	Treatment arms	Comparison group		
		versus A	versus B	versus C
Incremental life years	B	0.93 (0.53–1.35)	–	Same as C versus B
	C	1.67 (0.99–2.35)	0.73 (0.23–1.24)	–
	D	6.93 (6.49–7.38)	5.99 (5.39–6.58)	5.26 (4.83–5.65)
Incremental QALYs	B	0.7 (0.37–1.11)	–	Same as C versus B
	C	2.49 (1.87–3.13)	1.78 (1.2–2.31)	–
	D	5.9 (4.28–7.17)	5.2 (3.51–6.44)	3.41 (2.27–4.26)
Incremental cost (in US$)	B	9449 (5496–14660)	–	Same as C versus B
	C	11,447 (8059–15853)	1998 (865–3264)	–
	D	44,545 (31,404–60,973)	35,096 (25,087–46,766)	33,097 (22,956–45,193)
Incremental cost (in US$) per QALY gained	B	14,071 (7474–24983)	–	Same as C versus B
	C	4652 (3052–6837)	1149 (440–2095)	–
	D	7669 (5011–11,701)	6906 (4497–10,988)	9948 (6287–16,568)
Incremental cost (in US$) per LY gained	B	10,522 (5917–18,721)	–	Same as C versus B
	C	7151 (4273–11,375)	3472 (9,41–9271)	–
	D	6432 (4502–8792)	5859 (4218–7833)	6291 (4374–8838)

US$: United States Dollar; QALY: Quality adjusted life years. *Figures in parentheses indicate 2.5th and 97.5th percentile.

Table 4: **Discounted probabilistic incremental outcomes of the treatment arms included in the base case analysis.**

Incremental outcomes*	Treatment arms	Comparison group	
		versus E	versus F
Incremental life years	F	1.89 (1.44–2.03)	–
	G	7.22 (6.74–7.68)	5.32 (5.16–5.47)
Incremental QALYs	F	1.56 (1.06–2.03)	–
	G	6.02 (4.41–7.22)	4.45 (3.19–5.29)
Incremental cost (in US$)	F	3407 (2486–4666)	–
	G	39,768 (27,510–54,979)	36,361 (24,410–51,090)
Incremental cost (in US$) per QALY gained	F	2237 (1452–3401)	–
	G	6711 (4423–10,245)	8291 (5249–12,969)

US$: United States Dollar; QALY: Quality adjusted life years. *Figures in parenthesis indicate 2.5th and 97.5th percentile.

Table 5: **Discounted probabilistic incremental outcomes of the treatment arms included in the scenario analysis.**

current market prices in India. Among the various therapeutic regimens for CLL treatment included in the present study, the CP as the first-line followed by BR as second-line therapy came out to be cost-effective at one time GDP per capita of India. The scenario analysis, excluding the impact of second-line therapy, also points to a similar conclusion and shows chlorambucil based regimen as a cost-effective first-line treatment in India. However, if the current price of either combination of BR & ibrutinib or even ibrutinib alone is reduced by more than 80%, regimen comprising of BR as first-line therapy followed by second-line ibrutinib starts to become the cost effective. Finally, based on the grounds of budget impact analysis (which is now an integral part of any HTA analysis) and from the point of view of reimbursement price that affects the claim pay out of a public insurance program, price reduction of both BR and ibrutinib by 80% seems to more financially sustainable and provides more value for money.

In India, a developing economy with limited health resources, type of treatment prescribed to the CLL patients does not parallel to those given in developed western nations. Currently there is no specific guidelines with regards to the management of CLL in India. The selection of the treatment arms in the present analysis was based on the real-world Indian evidence which showed that chlorambucil plus prednisolone (CP) is the commonly prescribed regimen, followed by bendamustine plus rituximab (BR) and other regimens including ibrutinib (prescribed to a minute group of patients) for the CLL treatment.[4] As around 54% of the health care expenses is borne OOP by patients in India, affordability of the treatment regimen and supportive care is an important criterion while finalizing the

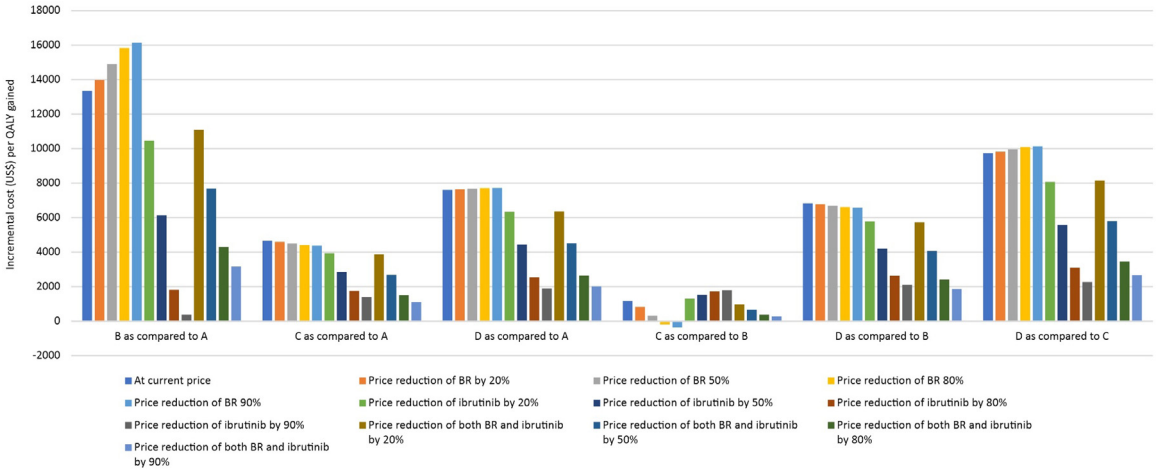

Fig. 3: **Threshold analysis.** Strategy 'A' consists of chlorambucil plus prednisolone as first-line therapy and bendamustine plus rituximab as second-line therapy, strategy 'B' comprises chlorambucil plus prednisolone as first-line therapy and ibrutinib as second-line therapy, strategy 'C' comprises of bendamustine plus rituximab as first-line therapy and ibrutinib as second-line therapy, strategy 'D' consists of ibrutinib as first-line therapy followed by bendamustine plus rituximab as the second-line therapy, BR: Bendamustine plus rituximab, US$: United States Dollar, QALY: Quality adjusted life years.

treatment regimen in addition to performance status and prognostic factors. The same has been reflected and captured in the real-world analysis. Only those in the upper rich quintiles or with some pre-payment mechanisms (i.e., health insurance), are able to avail the treatment based on the National Comprehensive Cancer Network (NCCN) guidelines, which is upgraded according to the higher effectiveness of new drugs. However, the treatment gets modified if there is limitation in finances. Currently, less than 20% of Indian population is covered under any private or social health insurance. The rest 50% are eligible to avail treatment under Government-sponsored health insurance of AB PM-JAY and the remaining 30% are altogether devoid of any type of health insurance.[46] With the exception to those who can afford it, the interventions that are affordable or provide best value for money starts to make more sense. Even AB PM-JAY, the largest single purchaser of health care to around 500 million citizens make use of the HTA evidence for the decision making around inclusion/exclusion of interventions in its health benefit package.[46,47]

As mentioned earlier, none of the previous economic evaluations has directly compared the three drugs (i.e., chlorabucil, bendamustin and ibrutinib) in question. However, there are previous studies that have compared either any 2 of the 3 drugs, or estimated the cost effectiveness of these drugs with other anti-CLL drugs.[12,16–21] The bendamustine-based therapy was reported to be the cost-effective strategy from most of the studies that compared bendamustine with other drugs.[12,16] As these studies were undertaken from the context of high-income countries, that have higher willingness to pay or cost effectiveness thresholds, might justify the dissimilarity in findings from the present study. However, ibrutinib not being a cost-effective therapy for the first-line treatment corroborates with the conclusion of other economic evaluations.[19,23] On the other hand, a study comparing first-line ibrutinib versus second-line and third line ibrutinib concluded that delaying ibrutinib for later lines is a cost-effective option instead of the first line use.[17] A cost analysis estimated that ibrutinib, when used as a first-line therapy, could increase the total cost of CLL treatment by around 0.3 US$ million compared to second-line therapy.[22] Our analysis on similar lines also shows that ibrutinib, when used as a second-line therapy in treatment arm C, provides more value for money as compared to ibrutinib as a first-line therapy in treatment arm D.

Although it is not entirely possible to 'adapt' or 'generalise' the findings of an economic evaluation to other country contexts, given the difference in the cost of health care delivery across nations. There are some novel methods, like adaptive or rapid HTA, that by using the concepts of purchasing power parity, estimate a cost-effective price of a drug for a particular country based on the findings of economic evaluation conducted for other country context.[48] However, these methods are still evolving and have not been fully validated. Nevertheless, one general recommendation for countries with similar socio-demographic and income levels to India, is that opting for either chlorambucil or bendamustine-based regimen as a first-line therapy and using ibrutinib for later second-line or third-line of treatment may provide more value for money.[17]

Model validation

The median survival time and survival rate of the arm E, chlorambucil alone for first-line treatment was compared with the local epidemiological data from India.[8] Our study reported a median survival time of 42 months and 5-year survival rate of around 25% following treatment with arm A. These model outcomes corroborate with the findings from an Indian prospective cohort study that reported a median survival time and 5- year survival rates of around 3.5 years and 25% respectively among those in the stage IV CLL.[8] As per study by Hillmen and colleagues, the PFS curves showed that 52% of patients were progression free at 12 months of treatment with chlorambucil. This finding also corroborates with the modelled output of our analysis which shows that 49% patients were progression-free at 12 months in treatment arm E. (Supplement material Fig. S25).[6] The modelled PFS curves for rest of treatment arms have also been included in the supplementary section: Figs. S21–S27.

Strength and limitations

The present study is first of its kind that has comprehensively analysed and compared not only the first-line anti-CLL drugs, but also assessed the cost-effectiveness of various combinations of first-line and second-line therapies. We used a lifetime horizon that appears to be justified considering longer survival of patients with CLL. We recognize that most of the clinical parameters were assessed from the existing RCTs that had limited follow up periods. This could further lead to uncertainty regarding the long-term outcomes beyond the trial period. We used parametric survival modelling to extrapolate post-trial time dependent probabilities, where feasible, to increase the accuracy of model outcomes. Furthermore, various sensitivity analyses were performed to measure the impact of parameter uncertainty. To simulate the real-world scenario, we also considered discontinuation of first-line therapy due to specific serious AE and modelled both disutility and costs associated with these AE.

The data on quality of life and OOP expenses was assessed from CaDCQoL, which makes our findings more reliable. Given the nature and availability of cancer treatment in India, we also included direct non-medical cost as well. In India, the cancer treatment is available at regional specialized tertiary care facilities and is not too

decentralised. Therefore, such non-medical expenditures on travel, food, accommodation contribute significantly to the total cost of cancer care. Evidence shows direct non-medical expenditures account for around 30% the total direct expenditure on cancer treatment in India.

The data from CaDCQoL shows that among the patients suffering from leukaemia, only half of them had health insurance or received some form of financial support and the remaining half had to pay out of pocker from savings or borrowings for the treatment. Given the extent of OOP payments in India, the burden of prolonged expenditure could impact the accessibility to timely treatment or supportive care and hence the treatment outcome. As CaDCQoL was a cross-sectional study with no prospective follow-up, data on future health outcomes was not collected. We recommend undertaking future studies estimating the difference in the health outcome among those who received any financial assistance and those who did not.

The present study was undertaken considering broader patient characteristics to ensure that the results can be generalized to a larger patient population. The input parameters were assessed from the latest clinical trials.[5,6,25,26] that have considered a mixed patient population and have ensured the inclusion of patients with characteristics like 17p deletion or 11q deletion. However, we do understand the need to undertake a separate sub-group analysis for specific groups of patients with specific prognostic factors or performance status. But, considering data constraints regarding the incidence of adverse effects and progression estimates, using first line and second line therapies among particular groups of patients makes the sub-group analysis a bit difficult.

Given the resource crunch in health sector, the decision-makers need to allocate resources judiciously where the evidence from economic evaluations becomes useful. Though the aim of our study is not to create standard clinical guidelines, we intend to inform the decision-makers about the economic and financial implications of choosing a particular line of CLL treatment in India. The study concludes that at the current market price of anti-CLL drugs included in the present study, regime comprising of CP as first-line followed by BR as second-line therapy is the most cost-effective strategy for treating CLL in India. Further, none of the regimen comprising of first-line BR or ibrutinib are cost-effective. However, if the prices of both BR and ibrutinib are reduced by 80%, strategy of BR as first-line and ibrutinib as second-line therapy becomes cost-effective in the Indian context.

Contributors

PN, ASC, PM and SP contributed to conception and design of the study, data analysis and interpretation and drafting the original manuscript. SP was responsible for arranging the financial support for the study. PN, ASC, PM, LK, AS, NG, NM, AM, ACK, SG and SP contributed to collection and assembly of data, interpretation of results, reviewing the final version of manuscript and final approval the manuscript. All authors are accountable for all aspects of the work.

Data sharing statement

All data generated or analysed during this study are included in this published article (and its supplementary information files).

Declaration of interests

Shankar Prinja has formerly served as the Executive Director at the National Health Authority, India. The authors declare no other conflict of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lansea.2023.100201.

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