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ORIGINAL RESEARCH

Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for treatment of chronic lymphocytic leukemia in Ukraine

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Olena Mandrik[1]
Isaac Corro Ramos[2]
Saskia Knies[1,3]
Maiwenn Al[1,2]
Johan L Severens[1,2]

[1]Institute of Health Policy and Management, Erasmus University Rotterdam, Rotterdam, the Netherlands; [2]Institute of Medical Technology Assessment (iMTA), Erasmus University Rotterdam, Rotterdam, the Netherlands; [3]National Health Care Institute, Diemen, the Netherlands

Abstract: The aim of this study was to assess the cost-effectiveness, from a health care perspective, of adding rituximab to fludarabine and cyclophosphamide scheme (FCR versus FC) for treatment-naïve and refractory/relapsed Ukrainian patients with chronic lymphocytic leukemia. A decision-analytic Markov cohort model with three health states and 1-month cycle time was developed and run within a life time horizon. Data from two multinational, prospective, open-label Phase 3 studies were used to assess patients' survival. While utilities were generalized from UK data, local resource utilization and disease-associated treatment, hospitalization, and side effect costs were applied. The alternative scenario was performed to assess the impact of lower life expectancy of the general population in Ukraine on the incremental cost-effectiveness ratio (ICER) for treatment-naïve patients. One-way, two-way, and probabilistic sensitivity analyses were conducted to assess the robustness of the results. The ICER (in US dollars) of treating chronic lymphocytic leukemia patients with FCR versus FC is US$8,704 per quality-adjusted life year gained for treatment-naïve patients and US$11,056 for refractory/relapsed patients. When survival data were modified to the lower life expectancy of the general population in Ukraine, the ICER for treatment-naïve patients was higher than US$13,000. This value is higher than three times the current gross domestic product per capita in Ukraine. Sensitivity analyses have shown a high impact of rituximab costs and a moderate impact of differences in utilities on the ICER. Furthermore, probabilistic sensitivity analyses have shown that for refractory/relapsed patients the probability of FCR being cost-effective is higher than for treatment-naïve patients and is close to one if the threshold is higher than US$15,000. State coverage of rituximab treatment may be considered a cost-effective treatment for the Ukrainian population under conditions of economic stability, cost-effectiveness threshold growth, or rituximab price negotiations.

Keywords: cost-effectiveness, rituximab, leukemia, Ukraine

Introduction

Chronic lymphocytic leukemia (CLL) is a progressive oncological disease characterized by the clonal proliferation and accumulation of neoplastic B lymphocytes in the blood, bone marrow, lymph nodes, and spleen. According to the Ukrainian National Cancer Register[1] the total morbidity rate for patients with diagnosed leukemia was 7.8 per 100,000 people. No national Ukrainian statistical data on CLL prevalence are available; however, if we assume the same distribution as in the US exists for the four major types of leukemia, up to 3.7 per 100,000 people are estimated to be CLL related.[2] The clinical course of this disease can be highly diverse and dependent on many factors, such as stage of the disease by Rai (from 0 to IV) and Binet (from A to C), chromosomal abnormalities, or mutations of the immunoglobulin heavy variable chain gene.[3–5]

Correspondence: Olena Mandrik
Institute of Health Policy and Management, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, the Netherlands
Tel +31 10 408 8525
Fax +31 10 408 9094
Email olena.dem@gmail.com

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With the exception of blood band marrow transplantation – which has significant limitations by age and comorbidities – CLL remains an incurable condition. According to the national treatment protocol in Ukraine[5] there is a number of treatment options for CLL patients. Besides the "watch and wait" strategy for patients with the asymptomatic state of CLL, monotherapies are currently available: cytotoxic drugs including alkylating agents (chlorambucil, cyclophosphamide, and bendamustine), antimetabolites or purine analogs (fludarabine or cladribine), mitoxantrone (an anthracycline) and prednisolone (a corticosteroid), as well as a number of therapeutic chemotherapy combination schemes.[3,5] One of the most frequently prescribed schemes for CLL patients treated in specialized hospitals of Ukraine is a fludarabine and cyclophosphamide scheme (FC).[6]

Rituximab, a monoclonal antibody that targets the CD20 cell surface antigen, is recommended for use in combination with chemotherapy for both treatment-naïve patients, refractory patients (those who experienced treatment failure or disease progress within 6 months of the last treatment) or patients who relapsed (those who experienced a response to therapy, but progressed after 6 or more months). Despite being one of the most expensive drugs used in CLL treatment in Ukraine, rituximab was included in the state tender purchases the previous years.[6,7] Adding rituximab to FC (FCR) has been shown to be a promising medical product according to clinical trial data on both previously treated and untreated CLL patients.[4,8]

The cost-effectiveness of FCR versus FC in treatment of naïve or refractory/relapsed patients was previously confirmed in Spain, the US, and the UK.[9–11] In Spain the incremental cost-effectiveness ratio (ICER) was €19,343 per quality-adjusted life year (QALY) gained for the first-line treatment and €24,781 for the second-line treatment over a 10-year horizon.[9] In the US study the ICER was US$23,530 per QALY considering a third-party payer and US$31,513 per QALY considering a societal perspective over the life time horizon.[10] In the UK rituximab was also considered to be a cost-effective option with an ICER of £13,189 per QALY for FCR versus FC in the treatment of naïve patient population; however its combination with other chemotherapy agents was not recommended by the National Institute for Health and Care Excellence.[11]

To the best of our knowledge no economic evaluation on rituximab use was performed in Ukraine, nor any other country of the Central and Eastern European or former Soviet region. Because of differences in treatment practice, perspectives, unit costs (including hospitalization), and demographic characteristics (both patients and general population), generalizability to Ukraine of the economic evaluations mentioned above is not possible. While no cost-effectiveness threshold has been established in Ukraine, the World Health Organization (WHO) considers technologies with a threshold of less than one GDP per capita to be very cost-effective, and those with a threshold of less than three GDP per capita to be cost-effective.[12] In 2013 the GDP per capita in Ukraine was equal to US$3,900, according to data of the World Bank.[13]

In sum, the aim of this study was to assess, from a health care perspective using a life time horizon, the cost-effectiveness of FCR compared to FC for treatment-naïve and refractory/relapsed Ukrainian CLL patients.

Methods

Framework/structure of the model

Two decision-analytic Markov cohort models with the same structure were developed in Microsoft® Excel 2007 to assess the incremental costs and benefits associated with FCR. These models were run on two populations using data from two randomized controlled trials, one with treatment-naïve and one with refractory/relapsed patients. Three health states were defined in the models with a cycle time of 1 month: 1) stable or progression-free state; 2) disease-progressed state; and 3) death. Assessment of the incremental costs and benefits from a health care perspective was conducted using a life time horizon. QALYs comprised the main outcome in both models with uniform 3% discounting for both costs and effects.[14]

Target population

We considered the modeled cohort of treatment-naïve patients to be identical to the trial population from a published prospective, open-label, Phase 3 study on 817 randomly assigned (1:1) patients carried out in 190 centers in eleven countries. Enrolled in this study were treatment-naïve patients diagnosed with immunophenotypically confirmed CLL in Binet stage C (31% in FC and 31% in FCR) or those with confirmed active disease in Binet stages A (5% in FC and 4% in FCR) or B (63% in FC and 64% in FCR). Mean age of patients was 61 years and 74% were males. Eastern Cooperative Oncology Group (ECOG) performance status of 0 was reported in 58% of FC and 56% of FCR groups.[4] (ECOG performance status is the criteria used to assess how the disease affects daily living abilities of patients, where "0" is a fully active person and "5" is dead [http://www.ecog.org/]).

The modeled cohort of refractory/relapsed patients was considered to be identical to the trial population from an international, multicenter, open-label, Phase 3 study on 552 randomly assigned (1:1) patients carried out in 88 centers in 17 countries. Patients who had received one prior line of therapy, such as single-agent chlorambucil (or combined with prednisone/prednisolone), single-agent fludarabine (or another nucleoside analog), or an alkylator containing combination regimen, but not an alkylator/nucleoside analog combination, were enrolled in that study. The distribution of CLL patients by confirmed Binet stages in this trial was as follows: stage C (31% in FC and 31% in FCR), stage A (11% in FC and 9% in FCR), and stage B (58% in FC and 60% in FCR). Mean age of patients was 62 years in FC and 63 in FCR groups, 66% (FC) and 68% (FCR) were males. An ECOG performance status of 0 was reported in 59% of FC and 61% of FCR groups.[8]

Treatment and treatment effect

According to trial data[4,8] and national clinical guidelines, CLL patients on FCR should receive the following doses of drugs during each cycle: fludarabine (25 mg/m^2/d), cyclophosphamide (250 mg/m^2/d) for 3 days, rituximab (375 mg/m^2 on day one of the first cycle and 500 mg/m^2 on day one of subsequent cycles). In the model, dose-per-patient was calculated using an average body surface among the Ukrainian population (1.86 m^2). We considered that the Markov cohort population did not receive full courses of therapy similar to the trial population,[4,8] so the final average doses of each drug were adjusted to the average consumed doses (by treatment adherence in trials) (Table 1).

Survival data

Overall survival and progression-free survival (PFS) were retrieved from the trials' publications presenting Kaplan–Meier plots.[4,8] The reported observation period equal to 61 months for treatment-naïve patients and to 57 months for previously-treated patient (52 months for PFS during FC treatment) was chosen.[4,8] There was no information available on characteristics of Ukrainian CLL patients by Binet stages and ECOG performance status. At the same time, by sex and age distribution Ukrainian CLL patients were similar to trial populations selected as clinical data sources.[4,6,8] Two parametric extrapolation methods were applied. A Weibull model was selected to incorporate monotonic hazards, while a log-logistic model was selected as an alternative to incorporate non-monotonic hazards. The model that provides the closest parametric estimation was selected for cohort survival assessment.

Costs

In line with recommendations of the International Society For Pharmacoeconomics and Outcomes Research taskforce report on transferability,[15] unit costs and resource utilization were retrieved from local sources. From the health care perspective, the following costs were included in the model: initial therapy costs, hospitalization costs, adverse events costs, and salvage costs (Table 1). Unit drug costs were included in the deterministic model by the most frequently prescribed trade names.[6] Unit drug prices were retrieved from the website of Ukraine's Ministry of Health.[16] Costs of grades 3 and 4 adverse events reported with a frequency greater than or equal to 5% were accounted for in the model calculations. Opinions of clinical experts from specialized institutions of Ukraine and hospital records were used to define the most frequently prescribed treatment schemes for these conditions A previously published costing study in Ukraine was used to assess costs of salvage treatment.[6] Because of data obsolescence, these costs were considered to grow by the consumer price index for pharmaceuticals and health care for the last 4 years (5.7%). Additionally, the model took into consideration the monthly growth in costs for salvage treatment proportional to an average monthly consumer price index for pharmaceuticals and health care (0.11875%).[17] Data of specialized hospitals in Ukraine were used to determine an average duration of hospitalization due to a relapse, as well as daily costs of hospital stay excluding pharmaceutical treatment.[6] Similar to pharmaceutical treatments, hospital stay unit costs were considered to grow proportionally to an average consumer price index for pharmaceuticals and health care. The exchange rate of the National Bank of Ukraine on June 4, 2014 (11,833 Ukrainian Hryvnia per US$) was used in all calculations.

Utilities

No country-specific utility data were available for CLL patients, nor for the general Ukrainian population, therefore, utilities of health states associated with CLL treatment (values of 0.78 for the progression-free or stable disease state and 0.68 for the progressed disease) were assumed generalizable from the UK.[18]

Sensitivity analyses and data transferability

We used sensitivity analyses to address uncertainty in the defined input parameters specific for Ukraine and those generalized from other populations. Using univariate analyses we assessed the impact of variations in rituximab costs,

Table 1. Resource use, costs, and utilities and patients' characteristic input data used in both deterministic and probabilistic models

Parameter	Deterministic analysis		Sensitivity analyses	
	Values	Comments and/or sources	Values	Comments and/or sources
Resource use				
Annual number of hospitalization days (for salvage patient), days	34	Analysis of the hospital records[6]	27.2–40.8	20% variation from deterministic value,[6] flat distribution
Refractory/relapsed patients				
Total dose of fludarabine received during 6 cycles of the therapy, mg	202.69	Trial dose adjusted to percentage of patients received therapy on each cycle[8] and body surface among Ukrainian population (1.86m^2)	186–279	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Total dose of cyclophosphamide received during 6 cycles of the therapy, mg	2,131.56	Trial dose adjusted to percentage of patients received therapy on each cycle[8] and body surface among Ukrainian population (1.86m^2)	1,860–2,790	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Total dose of rituximab received during 6 cycles of the therapy, mg	4,854.60	Trial dose adjusted to percentage of patients received therapy on each cycle[8] and body surface among Ukrainian population (1.86m^2)	3,720–5,580	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Treatment naïve patient				
Total dose of fludarabine received during 6 cycles of the therapy (patients on FC treatment), mg	223.2	Trial dose adjusted to average number of cycles received by the patients in the trial[4] and body surface among Ukrainian population (1.86m^2)	186–279	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient , flat distribution
Total dose of cyclophosphamide received during 6 cycles of the therapy (patients on FC treatment), mg	2232	Trial dose adjusted to average number of cycles received by the patients in the trial[4] and body surface among Ukrainian population (1.86m^2)	1,860–2,790	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Total dose of fludarabine received during 6 cycles of the therapy (patients on FCR treatment), mg	241.8	Trial dose adjusted to average number of cycles received by the patients in the trial[4] and body surface among Ukrainian population (1.86m^2)	186–279	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Total dose of cyclophosphamide received during 6 cycles of the therapy (patients on FCR treatment), mg	2418	Trial dose adjusted to average number of cycles received by the patients in the trial[4] and body surface among Ukrainian population (1.86m^2)	1,860–2,790	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Total dose of rituximab received during 6 cycles of the therapy (patients on FCR treatment), mg	4,231.5	Trial dose adjusted to average number of cycles received by the patients in the trial[4] and body surface among Ukrainian population (1.86m^2)	3,487.5–5,347.5	Calculated dose required to receive 4 to 6 cycles of the therapy by Ukrainian patient, flat distribution
Unit costs				
Fludarabine costs, US$ per mg	3.31	Costs of drugs the most frequently prescribed via state budget[6]	1.89–3.31	Analyzed range of costs available on the state market,[a] flat distribution
Cyclophosphamide costs, US$ per mg	0.0022	Costs of drugs the most frequently prescribed via state budget[6]	0.0022–0.036	Analyzed range of costs available on the state market,[a] flat distribution
Rituximab costs, US$ per mg	2.24	Costs of drugs the most frequently prescribed via state budget[6]	1.76–2.24	Analyzed range of costs available on the state market,[a] flat distribution
Hospitalization costs per day, US$	16	Cost of hospitalization stay in specialized hospital of Ukraine, 2010[6,17]	13–19	20% costs variation, flat distribution

Salvage therapy costs[b], US$ per month	177.06	Cost of relapse treatment in specialized hospital of Ukraine, 2010[6,17]	141.64–212.47	20% costs variation, flat distribution
Average monthly index of consumption prices	0.1188%	Calculated as average from the last 4 years[17]	NA	NA
Average body surface	1.86	Average body surface in Ukraine	NA	NA
Side effects costs				
Average cost per treatment naïve patient (FC), US$	74	Average costs by the most frequently prescribed trade names (hospital cards analysis[6] and expert's opinion)	64–248	Minimum and maximum costs by prices for each generic name, registered on the website of the Ministry of Health, flat distribution[16]
Average cost per treatment naïve patient (FCR), US$	106	Average costs by the most frequently prescribed trade names (hospital cards analysis[6] and expert's opinion)	96–335	Minimum and maximum costs by prices for each generic name, registered on the website of the Ministry of Health, flat distribution[16]
Average cost per refractory/relapsed patient (FC), US$	67	Average costs by the most frequently prescribed trade names (hospital cards analysis[6] and expert's opinion)	58–194	Minimum and maximum costs by prices for each generic name, registered on the website of the Ministry of Health, flat distribution[16]
Average cost per refractory/relapsed patient (FCR), US$	68	Average costs by the most frequently prescribed trade names (hospital cards analysis[6] and expert's opinion)	60–182	Minimum and maximum costs by prices for each generic name, registered on the website of the Ministry of Health, flat distribution[16]
Utilities				
Progression-free survival	0.78	Average value[18]	0.75–0.82	Confidence interval, normal distribution[18]
Overall survival	0.68	Average value[18]	0.64–0.72	Confidence interval, normal distribution[18]
Survival analysis: refractory/relapsed patients				
Progression-free survival FC scheme				
Lambda	0.01958	Weibull estimation from Kaplan–Meier curve[8]	±0.001381	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Gamma	1.15346	Weibull estimation from Kaplan–Meier curve[8]	±0.020872	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Correlation coefficient	–0.99051400	Weibull estimation from Kaplan–Meier curve[8]	NA	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Overall survival FC scheme				
Lambda	0.00436	Weibull estimation from Kaplan–Meier curve[8]	±0.000742	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Gamma	1.24444	Weibull estimation from Kaplan–Meier curve[8]	±0.046098	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Correlation coefficient	–0.99598300	Weibull estimation from Kaplan–Meier curve[8]	NA	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Progression-free survival FCR scheme				
Lambda	0.02847	Weibull estimation from Kaplan–Meier curve[8]	±0.00237	Weibull analysis from Kaplan–Meier curve,[8] normal distribution

(*Continued*)

Table 1. (*Continued*)

Parameter	Deterministic analysis		Sensitivity analyses	
	Values	Comments and/or sources	Values	Comments and/or sources
Gamma	0.95491	Weibull estimation from Kaplan–Meier curve[8]	±0.024185	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Correlation coefficient	−0.99062300	Weibull estimation from Kaplan–Meier curve[8]	NA	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Overall survival FCR scheme				
Lambda	0.00594	Weibull estimation from Kaplan–Meier curve[8]	±0.00039	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Gamma	1.09334	Weibull estimation from Kaplan–Meier curve[8]	±0.017784	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Correlation coefficient	−0.99524000	Weibull estimation from Kaplan–Meier curve[8]	NA	Weibull analysis from Kaplan–Meier curve,[8] normal distribution
Survival analysis: treatment naïve patients				
Progression-free survival FC[a] scheme				
Lambda	0.013576	Weibull estimation from Kaplan–Meier curve[4]	±0.000681	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Gamma	0.000681	Weibull estimation from Kaplan–Meier curve[4]	±0.013858	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Correlation coefficient	−0.99259	Weibull estimation from Kaplan–Meier curve[4]	NA	NA
Overall survival FC[a] scheme				
Lambda	0.000994	Weibull estimation from Kaplan–Meier curve[4]	±0.042679	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Gamma	1.511907	Weibull estimation from Kaplan–Meier curve[4]	±0.042679	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Correlation coefficient	−0.99722	Weibull estimation from Kaplan–Meier curve[4]	NA	
Progression-free survival FCR[b] scheme				
Lambda	0.005851	Weibull estimation from Kaplan–Meier curve[4]	±0.000451	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Gamma	1.219618	Weibull estimation from Kaplan–Meier curve[4]	±0.020593	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Correlation coefficient	−0.99513	Weibull estimation from Kaplan–Meier curve[4]	NA	NA
Overall survival FCR[b] scheme				
Lambda	0.000213	Weibull estimation from Kaplan–Meier curve[4]	±0.00014	Weibull analysis from Kaplan–Meier curve,[4] beta distribution
Gamma	1.809901	Weibull estimation from Kaplan–Meier curve[4]	±0.168617	Weibull analysis from Kaplan–Meier curve,[4] normal distribution
Correlation coefficient	−0.99808000	Weibull estimation from Kaplan–Meier curve[4]	NA	NA

Notes: [a]Unit drug prices were retrieved from the website of Ukraine's Ministry of Health.[16] [b]Monthly salvage costs were calculated from a previous study on cost-of-treatment of CLL in Ukraine by recalculating the annual costs to monthly costs.[6] The received costs were assumed to grow from the time of the assessment on consumer price index for pharmaceuticals and health care for the last 4 years. Each time the conversion of the costs was conducted from local currency (Ukrainian Hryvnia).

Abbreviations: CI, confidence interval; FC, fludarabine and cyclophosphamide scheme; FCR, rituximab with fludarabine and cyclophosphamide scheme; CLL, chronic lymphocytic leukemia; NA, not applicable.

hospitalization costs, salvage treatment costs, costs of side effects, average monthly index of consumption prices and discount rates. Multivariate analysis was applied because the UK data on utilities for different cancer states were generalized to the Ukrainian population for whom local data was absent.

The two trials used a multinational sample as a source of survival data for Markov cohort CLL patients.[4,8] Although the patient's country of enrollment in the trials was not reported, we assume that most were enrolled in countries with developed economies, where life-duration of the general population differs from those in Ukraine. Therefore we report an alternative scenario with Ukraine-specific mortality rate for non-CLL related causes to assess the impact of this parameter on the ICER. For this the sex- and age-specific difference in death probability among general population in the US and Ukraine was calculated. For this the difference in death probabilities between US and Ukrainian males and females of different age was calculated first using national statistical data.[19,20] Afterward, the death probability among the population identical to the cohort by sex and age characteristics was retrieved. As the next step the overall survival and PFS from the trial were added to the positive or negative coefficient of the difference in mortality depending on the patient's age at initiation of therapy. The survival analysis with Weibull extrapolation was performed on the received adjusted data to ensure higher reliability of the received results.

Additional scenario analyses were conducted to assess the impact of survival analysis on cost-effectiveness results. We varied duration of patients' observation period in the trials and assessed impact of these changes on the results of survival analysis and economic evaluations. Probabilistic sensitivity analyses with 5,000 runs were conducted to define overall uncertainty of the model. Both deterministic and probabilistic model parameters are presented in Table 1.

Results

Treatment with rituximab resulted in both a longer expected survival and a gain in QALYs compared to the standard therapy (Table 2). The gain in expected number of life years was 1.60 for both treatment-naïve and refractory/relapsed patients treated with the FCR versus FC in the base-case scenario. Associated costs were higher with FCR rather than FC treatment in the base case and all alternative scenarios (Table 2). The difference in QALYs gained and costs was smaller in the scenarios where survival analysis was conducted on the trial data with the longer follow-up (and the opposite). When survival data on treatment-naïve patients were extrapolated to 65 months, the incremental value of QALYs became negative. There was a smaller observed difference in both QALYs and costs for the FC and FCR treatment-naïve population, when adjustment to the expected higher mortality among the general population of Ukraine was conducted.

For every expected QALY gained, US$8,704 will be needed in the base-case scenario for state coverage of treatment-naïve patients, which can be considered a cost-effective option. The ICER of treating refractory/relapsed patients with FCR is close to the cost-effectiveness threshold within the base-case scenario (ICER US$11,056; threshold of three GDP per capita is US$11,700). The ICER of FCR use for treatment-naïve patients will be close to US$13,000 if a higher mortality among the general population in Ukraine is considered in the survival analysis. This ICER for treatment-naïve patients is above the theoretical cost-effectiveness threshold in Ukraine.

As can be seen from Table 3, an increase in the average consumer price index and discount rate caused a higher

Table 2 Cost-effectiveness analysis of adding rituximab to fludarabine plus cyclophosphamide scheme in treatment-naïve and refractory/relapsed patients: base-case and scenario analyses

	Cost difference	QALY difference	ICER (US$/QALY)
Treatment-naïve patients			
Base-case scenario FCR versus FC	US$10,827	1.24	US$8,704
Scenario 1: Ukraine-specific mortality among general population	US$8,022	0.62	US$12,897
Scenario 2: 56 months survival data	US$16,881	2.61	US$6,475
Scenario 3: 60 months survival data	US$15,204	2.22	US$6,851
Scenario 4: 62 months survival data	US$7,677	0.62	US$12,343
Scenario 5: 65 months extrapolated survival data	US$4,786	–0.83	Dominated
Treatment-experienced patients			
Base-case scenario FCR versus FC	US$13,081	1.18	US$11,065
Scenario 1: 52 months survival data, ICER (US$ per QALY)	US$ 14,660	1,53	US$9,557

Abbreviations: FC, fludarabine and cyclophosphamide scheme; FCR, rituximab with fludarabine and cyclophosphamide scheme; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

Table 3 Univariate and multivariate sensitivity analysis: impact of costs variations on cost-effectiveness results

Parameters of variation and values	ICER treatment-naïve patients		ICER treatment-experienced patients	
	US$/QALY	% of change from base ICER	US$/QALY	% of change from base ICER
Average monthly index of consumption prices				
0%	US$8,501	2%	US$10,677	4%
0.2375% (double from deterministic value)	US$8,907	–2%	US$11,453	–4%
Discounting, annual				
0%	US$6,904	21%	US$8,754	21%
5%	US$10,194	–17%	US$13,010	–18%
10%	US$15,041	–73%	US$19,494	–76%
Multivariate (discounting and average monthly index of consumption prices)				
0%	US$6,645	24%	US$8,297	25%
Doubled from deterministic value	US$11,184	–28%	US$14,440	–31%
Rituximab costs				
50% from deterministic costs	US$4,538	48%	US$6,471	42%
25% from deterministic costs	US$2,455	72%	US$4,173	62%
120% from deterministic costs	US$10,371	–19%	US$12,903	–17%
Hospitalization costs				
50% from deterministic costs	US$8,673	0%	US$10,895	2%
25% from deterministic costs	US$8,657	1%	US$10,810	2%
120% from deterministic costs	US$8,717	0%	US$11,133	–1%
Salvage therapy costs				
50% from deterministic costs	US$8,563	2%	US$10,298	7%
25% from deterministic costs	US$8,492	2%	US$9,914	10%
120% from deterministic costs	US$8,761	–1%	US$11,372	–3%
Side effects costs (FCR)				
50% from deterministic costs	US$8,662	0%	US$11,036	0%
25% from deterministic costs	US$8,640	1%	US$11,022	0%
120% from deterministic costs	US$8,722	0%	US$11,076	0%
Utilities				
Utility score 0.78 for progressed state and 0.88 for progression-free state	US$7,710	11%	US$9,744	12%
Utility score 0.58 for progressed state and 0.68 for progression-free state	US$9,993	–15%	US$12,800	–16%
Utility score 0.58 for progressed state and 0.88 for progression-free state	US$7,786	11%	US$10,838	2%

Abbreviations: FCR, rituximab with fludarabine and cyclophosphamide scheme; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio.

ICER for both treatment-naïve and refractory/relapsed patient populations. Similarly, multivariate analyses with zero values for both discounting and average monthly index of consumer prices resulted in ICERs of US$6,645 and US$8,297, respectively. Rituximab cost was the only cost parameter having a significant impact on the ICER in both populations. Changes in utilities had a moderate impact on cost-effectiveness results.

The results of probabilistic sensitivity analysis showed a high probability for FCR treatment to be cost-effective for both treatment-naïve patients (cost difference US$13,118, standard deviation [SD] US$8,079; QALYs difference 2.21, SD 1.78; ICER US$5,938) and refractory/relapsed patients (cost difference US$14,290, SD US$2,455; QALYs difference 1.68, SD 0.45; ICER US$8,485) with the threshold of US$11,000 (Figure 1). As the threshold value increases, the probability of FCR being cost-effective is higher for refractory/relapsed patients. In particular, when the threshold is higher than US$15,000, the probability of FCR being cost-effective converges to one for refractory/relapsed patients and to 0.80 for treatment-naïve patients (Figure 2).

Discussion

Neither for treatment-naïve nor for refractory patients is FCR a cost-effective option when using a threshold of US$3,900.[13] However, use of FCR can still be considered a cost-effective option when using the theoretical threshold of three times the GDP per capita in Ukraine. As such, we conclude that providing this drug should not be considered the highest priority, but should depend on budget availability. This conclusion

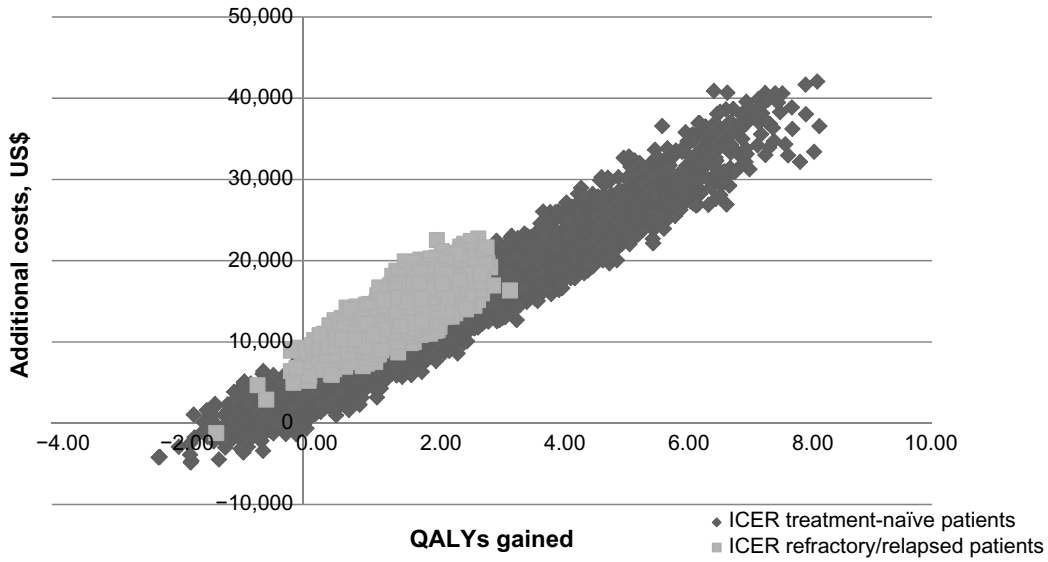

Figure 1 Cost-effectiveness plane: adding rituximab to treatment of naïve and refractory/relapsed patients.
Abbreviations: QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio.

is supported by the decision uncertainty demonstrated by the sensitivity analyses; thus, the state coverage of this drug for both treatment-naïve and refractory/relapsed population remains a possibility to be argued.

The Ukrainian Ministry of Health purchases rituximab annually for CLL patients' needs without recommendations on its actual use. Nearly US$1.4 million of the state budget was spent on rituximab purchase in 2013.[7] However, based on current evidence there is a higher rationality for it to be provided for the treatment-naïve patient population, rather than for refractory/relapsed patients. At the same time, if the theoretical threshold will become higher as a result of an improving Ukrainian economy, then coverage of refractory/relapsed patients is likely to become a more cost-effective option than that for the treatment-naïve population, an outcome primarily related to the higher stability of the results. On the other hand, in an unstable economic environment, FCR treatment of refractory/relapsed patients may not be a cost-effective option from a health care perspective, taking into account that any increase in the discount rate, treatment

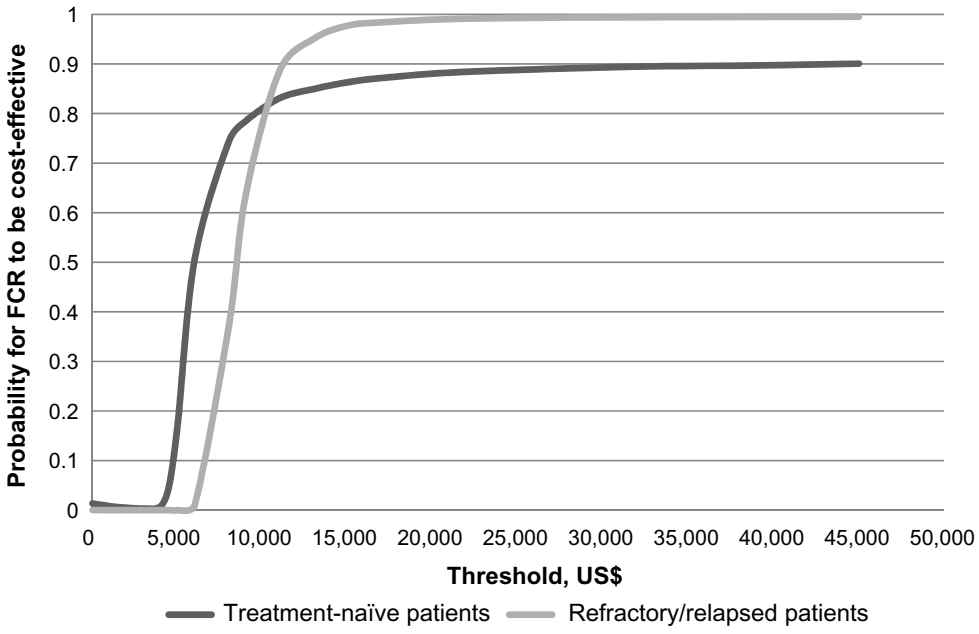

Figure 2 Cost-effectiveness acceptability curves.
Abbreviation: FCR, rituximab with fludarabine and cyclophosphamide scheme.

costs, or inflation rate (index of consumer prices) leads to an ICER estimate close to or above the value of the theoretical threshold. Because rituximab cost was the most influential parameter, price negotiation may be applied to ensure that state spending on this treatment is rational.

Because multinational clinical data were used for both models, we were concerned with how representative the trial population would be for Ukraine. While published data were used to populate the models, the cohort population in both models was not different by sex and age characteristics from both trial population and profiles of CLL patients in Ukraine in terms of mean age of naïve patients (60.3), age of refractory/relapsed patient (62.8), and the fact that 67% of patients were male.[6] Moreover, we considered that because of differences in age at diagnosis between different countries, if trial data were primarily retrieved from economically developed countries, the mortality from other causes in CLL trial population may be different from those in Ukraine. We conclude that if such a case exists, then it is doubtful that the use of rituximab in CLL population in Ukraine will be cost-effective.

As stated in the introduction, until now the cost-effectiveness of rituximab was assessed only in health care settings of economically more developed countries, such as the US,[10] the UK,[11] and Spain.[9] While all studies used three-stage models, the perspectives, model durations, and data extraction approaches differed. Methodological differences and non-generalizability of data limited transferring results of these studies to Ukraine. The third-party perspective is not applicable for Ukraine and, because of the significant number of assumptions,[10] the societal perspective also is not considered. Additionally, the use of parametric extrapolation methods for survival analysis instead of raw trial data was considered important because of the high impact of survival parameters on the ICER. While no relation between the country's income expressed by GDP per capita and the cost-effectiveness of FCR in comparison to FC has been shown in prior research,[9–11] in our study we see a significant difference in the values of the ratios observed. We also note an important similarity between our study and one conducted in the Spanish health care setting;[9] namely, treating treatment-naïve patients with FCR appeared to be more cost-effective than for refractory/relapsed patients.

Limitations

As a limitation we should point out that data pertaining to the trial population and the mortality rate from non-CLL causes among trial populations were not available, thus may not correspond to the Ukrainian population. Moreover, Ukrainian costs data are limited and based on one study assessment.

Conclusion

State coverage of rituximab treatment may not be considered a cost-effective treatment option for the Ukrainian population compared to current care; however, it may become cost-effective under conditions of economic stability, cost-effectiveness threshold growth or rituximab price negotiations. Taking into account the WHO recommendations on cost-effectiveness thresholds and current GDP per capita in Ukraine, state coverage of FCR for treatment-naïve patients is more economically argued than that for refractory/relapsed patients.

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Disclosure

Olena Mandrik has worked for different pharmaceutical companies, none of which is related to the production of the study drug or to the study itself. The authors have no other conflict of interests to declare.

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