



ORIGINAL
RESEARCH

Budget Impact analysis of the first-line treatment of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) adult patients

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ABSTRACT

BACKGROUND: Tyrosine kinase inhibitors (TKI) have dramatically improved survival in chronic myeloid leukemia in chronic phase (CML-CP), with a high percentage of patients reaching a major molecular response (MMR). Recently, several clinical trials demonstrated that some patients with CML-CP who achieve a sustained MMR on tyrosine kinase inhibitor (TKI) therapy can safely discontinue their therapy and attempt treatment-free remission (TFR).

Objective: The aim of the study was to evaluate the clinical and economic impact of TFR in naïve patients with CML-CP who start treatment with nilotinib, imatinib or dasatinib as first-line therapy, from the perspective of the Italian National Health Service (NHS).

METHODS: An Excel-based budget impact model was developed, in order to estimate the costs of the patients in first-line pharmacological treatment with CML. A specific Markov model was built, to simulate seven years of treatment with different TKIs. A systematic literature review was carried out, to identify the epidemiological and economic data, which were subsequently used to inform the model. The model considers two scenarios: 1) a Standard of Care (SoC) scenario, with the current estimated distribution of patients over the various TKI treatment, versus 2) an innovative scenario, characterized by an increase in the use of nilotinib (+28%) and generic imatinib (+35%) and a decrease in the use of dasatinib (-17%). A one-way deterministic sensitivity analysis was performed, in order to consider the variability of the results as a function of the main parameters considered in the model.

RESULTS: The model estimated that 775 patients with CML-CP could be treated with a TKI as first-line drug. The innovative scenario could increase TFR patients by approximately 60% and reduce the costs by more than € 30 million over 7 years. The increase in the use of nilotinib and the generic imatinib would generate a significant expenditure reduction.

CONCLUSIONS: This study demonstrates the economic effects of discontinuing TKIs in CML-CP patients. The increase in the use of nilotinib and the generic imatinib could generate an increase in the number of patients who achieve TFR, as well as an actual cost reduction.

Keywords

Tyrosine kinase inhibitors; Chronic myeloid leukemia; Budget Impact Model; Treatment-free remission

INTRODUCTION

Philadelphia chromosome-positive (Ph+) Chronic Myeloid Leukemia (CML) is a clonal disorder characterized by a genetic defect of the hematopoietic stem cells, which causes the proliferation and progressive accumulation of granulocyte cells in the bone marrow [1,2]. Granulocyte cells accumulate at first in the bone marrow and, at a later stage, in the blood and other organs.

To date, CML has an annual frequency of 1-2 new cases per 100,000 adults, and accounts for 15% of the total incidence of leukemia. Globally, the average age at diagnosis is between 45 and 55 years, while in Italy it's 60 years [3].

The natural history of the disease can be classified into three main and progressive phases: the chronic phase (CP), in which the disease is less aggressive and has a variable duration

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of 3-5 years; the accelerated phase (AP), a short, intermediate phase characterized by a different clinical symptomatology; and the blast phase (BP) – or crisis –, a stage where the disease is acute and terminal [3,4]. At the time of diagnosis, approximately 85% of patients are in the chronic phase, while in the remaining 15% a more advanced disease phase is already evident [4].

The current treatment of CML involves the use of tyrosine kinase inhibitors (TKIs): these greatly improved the survival of patients, whose life expectancy – from an average of 5-7 years at the end of the 1990s – has now been increased to over 25 years post-diagnosis [5].

Currently, guidelines recommend three drugs for the initial management of a newly diagnosed CML-CP patient: imatinib, dasatinib, and nilotinib.

Imatinib was the first TKI class drug approved by the US Food and Drug Administration for the treatment of CML-CP [3]. In the following years, second-generation TKIs – dasatinib and nilotinib – were introduced, all showing the ability to induce molecular and cytogenetic responses in patients who had failed therapy with imatinib. Over the years, several trials demonstrated the superiority of nilotinib and dasatinib vs imatinib in the first-line treatment; these two drugs were associated to a higher rate of major molecular response (MMR) and deep molecular responses (MR^{4.0} and MR^{4.5}), and to a lower percentage of progression of the chronic phase to the most advanced disease stages [6-8]. In light of these clinical trials, both dasatinib and nilotinib were authorized for the first-line treatment of CML, and the current European Leukemia Net guidelines, published in 2013, provide equal recommendations for the use of imatinib, dasatinib or nilotinib [9].

In the majority of cases, first-line therapy quickly eliminates leukemia cells: generally, the clinical picture and the blood count return to normal (full hematological remission) within the first few months of treatment. However, this does not imply the total eradication of the disease: a large proportion of leukemic cells survive, and can be identified through more sophisticated analytical methods. Therefore, even after a full hematological remission, therapy should be continued for years, first of all in order to achieve the MMR, and subsequently to allow the patient to achieve deep molecular responses (MR^{4.0} and MR^{4.5}), so that the progression to the advanced stages of the disease can be avoided as much as possible [10].

Based on recent knowledge, therapy had to be continued indefinitely; however, the pos-

sibility is being explored of discontinuing treatment in patients who have reached deep and stable molecular response levels. This possibility – not even contemplated until a few years ago – has now been accepted and officially registered for nilotinib, thanks to the results of the ENESTfreedom clinical study [7]. The aim of this study was to evaluate the potential for TFR (treatment-free remission) following frontline nilotinib treatment. After a median time of first-line treatment with nilotinib of approximately 3 and a half years, more than half (51.6%) of the 190 patients who achieved a sustained deep molecular response were able to discontinue therapy, while remaining in full remission for 48 weeks, the time period over which the primary endpoint was evaluated. These results are confirmed at longer follow up with a TFR rate equal to 49% at 96 weeks [11]. At present, the possibility of discontinuing therapy theoretically exists also for patients treated with imatinib and dasatinib, but this possibility is not officially registered for these drugs, nor is it suggested in the current guidelines, and therefore it is still confined to clinical trials.

When selecting a TKI frontline therapy, several factors must be considered: in addition to the efficacy and safety profile of each available treatment option, treatment cost can be an important consideration, particularly with the introduction of generic imatinib. The increased potential for TFR eligibility with nilotinib (and the potential cost-savings through treatment discontinuation) may be additional factors to consider for some patients when selecting a frontline TKI. These long-term considerations are increasingly important as patients with CML now have a life expectancy comparable to that of the general population.

The aims of this analysis are: to evaluate the therapeutic pathway of newly diagnosed Philadelphia chromosome-positive CML (Ph+ CML) patients on first-line treatment with imatinib (400 mg once daily), nilotinib (300 mg twice daily), or dasatinib (100 mg once daily); to quantify the economic impacts generated by TFR following nilotinib in the first-line treatment of Ph+ CML patients and to estimate the economic sustainability that could be obtained from the disinvestment generated by the generic imatinib.

METHOD

In order to calculate the estimated costs of CML patients on first-line treatment with TKI drugs, an Excel-based Budget Impact model, able to simulate the therapeutic pathway of the patients undergoing treatment with the

drugs studied (nilotinib, imatinib, dasatinib) was developed. For the implementation of the model, the guidelines recommended by the International Society of Pharmacoeconomics and Outcome Research (ISPOR) were followed [12,13]. To obtain the parameters for the model implementation and the calculation of the expenditure due to the treatment of CML, a systematic review of the literature was carried out, by examining publications that analyze, describe and compare epidemiological and/or economic evaluation studies on the TKIs of interest.

Identification of the population eligible for treatment

The first phase of the analysis focused on identifying the population eligible for the drugs under study, i.e. patients with newly diagnosed, not-yet-advanced CML-CP.

In particular, to the population resident in Italy in 2016 [14], the rate of incidence of the disease was applied (1-2 cases per 100,000 [3]). The model assumes that, out of the 912 diagnosed patients, 15% are not eligible for treatment, since they have been identified in an already advanced stage of the disease [4]. Through this method, it is estimated that, in Italy, the number of patients annually diagnosed and treated with a TKI is 775.

Therapeutic pathways projection

In the second phase, a Markov model was developed to represent the disease progression in patients diagnosed with CML and treated with TKIs (Figure 1) [15]. The model, consi-

sting of 17 discrete and complementary health states, is based on the stratification of patients in different health conditions, modeled on the basis of the 33 transition probabilities (with six-month cycles) used to populate the model. The model and the probabilities used to populate the Markov model and to estimate the Markovian traits have been discussed and validated by clinical experts.

In detail, the model provides for the possibility of initiating treatment with one of the drugs considered in the analysis that will produce, with different probabilities, an MMR, a sub-optimal response or a disease progression (AP/BC). This section of the model is defined by one six-month cycle and represents the starting therapy phase (start), in which patients spread over the various disease states. If the patient reaches a molecular response, he has the potential to achieve a deep molecular response (MR^{4.5}) and maintain it for up to 4 years (Markovian tunnel highlighted by the blue area). If the deep response persists until the fourth year of therapy, there will be the possibility (for the therapies that include it) to reach the discontinuation of therapy (TFR). Once the TFR has been reached, the model provides for the possibility of entering a persistent discontinuation state, or resuming treatment with a deep response. For the MMR state and each MR^{4.5} state, the model provides a limited switch chance. If the patient starts a disease progression (AP/BC), the chances are the treatment switch or the allogeneic transplantation. Death due to the disease can occur only in advanced stage patients.

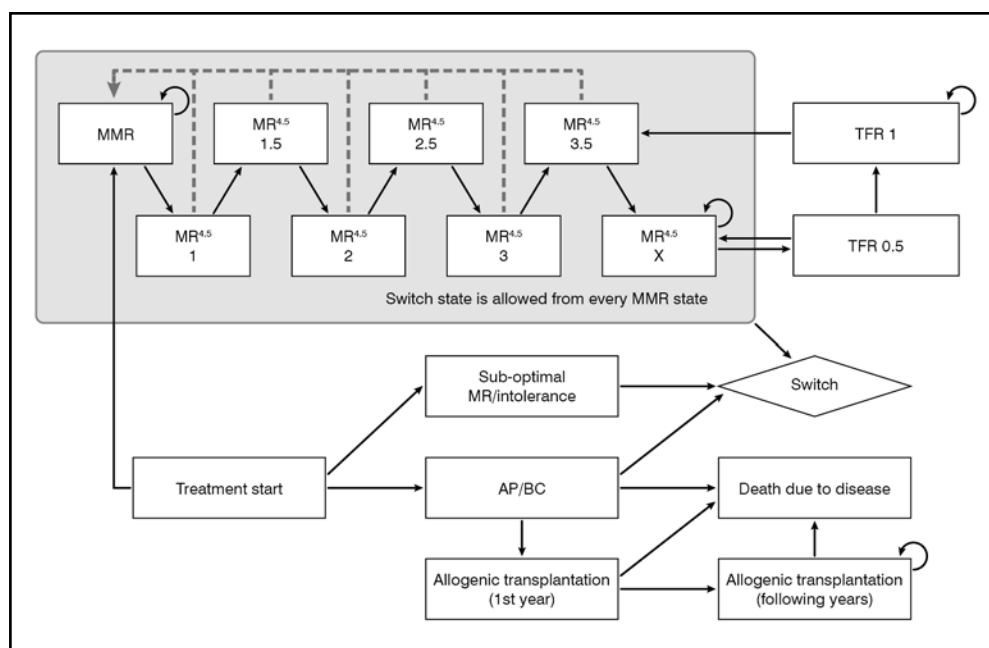


Figure 1. Markov model structure

AP/BC = disease progression; MR^{4.5} = deep molecular response; MMR = major molecular response; MR = molecular response; TFR = treatment-free remission

	Transition probabilities (%)						Source
	MMR	MR ^{4,5}	AP/BC	Death	Eligible for TFR	TFR confirmed (6 months after)	
Nilotinib	73.4	31.6	0.7	1.4	88.4	51.6	[6,7]
Imatinib	54.1	17.8	3.5	0.4	52.0	56.0	[6,7]
Dasatinib	68.1	32.8	3.3	1.6	0.0	0.0	[6,8]

Table I. Evidence from the pivotal trials used to estimate the probabilities in the model

AP/BC = disease progression; MR^{4,5} = deep molecular response; MMR = major molecular response; TFR = treatment-free remission

These successive phases of the model are represented as annual cycles (Year 1-Year 7).

Estimate of the model probabilities

In order to calculate the probabilities of transition in the first simulation cycle, it was decided to consider the evidence presented in the ENESTnd, ENESTFreedom and DASISION clinical studies (Table I). In particular, the ENESTnd study [6] enrolled 283 patients treated with nilotinib 300 mg twice daily, 281 patients treated with nilotinib 400 mg twice daily and 283 patients treated with imatinib 400 mg once daily. Observation of these patients allowed to obtain estimates of the probabilities of response to the treatment and progression of the disease for nilotinib and imatinib 3 years after the start of treatment. The model assumes that the response and/or the progression are concentrated in the first 6 months from the start of therapy (assumption related to the time lag of the Markovian model). In the absence of a direct comparison between nilotinib, imatinib and dasatinib, the probability of response and progression of dasatinib was estimated through the response and progression relative risks recorded in the DASISION study (head-to-head comparison between imatinib and dasatinib) [8], applied to the transition probabilities estimated for imatinib by the ENESTnd study [6].

TRF estimates were derived from the ENESTFreedom study [7] and modeled through the support of the expert opinion. For the implementation of the model, to the original probabilities appropriate changes and adaptations were applied, that can be found in Appendix A.

Treatment	Patients distribution (%)	
	Base case	Alternative scenario
Nilotinib	32	50
Imatinib (originator)	46	0
Dasatinib	22	5
Imatinib (generic)	0	45
Total	100	100

Table II. Analysis scenarios

Time horizon and analysis scenarios

According with the aim of the analysis, the model considered a seven-year simulation time horizon from the beginning of treatment, in order to appreciate the effects of the TFR in terms of health and economic impacts. This is in line with the ISPOR guidelines which state that a time horizon longer than a few years «may be needed to illustrate the offsetting disease cost-savings from the intervention that may occur in future years» [13]. Two distribution scenarios of the strategies analyzed were compared. In particular, in the base case, it is assumed that patients are distributed by treatment on the basis of what indicated in Table II, and that this distribution represents a realistic approximation of the strategies currently adopted in Italy. In this scenario, the possibility to reach TFR and the use of the generic imatinib is not provided for, so that the combined effects of the two innovations can be quantified. The alternative scenario hypothesizes that the disinvestment generated by the switch from branded imatinib to generic imatinib, and the possibility of an early discontinuation of treatment (TFR), allow a gradual increase in the number of patients treated with nilotinib (+18%, Table II).

Cost parameters

The costs considered in the model refer to the direct health costs associated with the management of CML-CP patients. As far as this type of cost is concerned, the data published by Lucioni et al. in 2015 [4] were mainly considered. The costs derived from the Lucioni study (Table III) [4] have been appropriately transformed to be consistent with the six-monthly cycles. For the cost of the switch, the aggregation of the various alternative treatments, in case the patient is intolerant or resistant to treatment, was used (Appendix A).

Statistical analyses

The results were represented as the net difference between the spending impact of the base case versus the spending impact of the

Cost parameters	Base case	Min	Max	Source
Pharmacological therapy and AT (€)				
Cost of therapy	1 year			
Nilotinib (year 1)	27,963			[16]
Nilotinib (year 2)	31,958			[16]
Imatinib (originator)	23,205			[17]
Imatinib (generic)	5,105			[18]
Dasatinib (year 1)	37,361			[16]
Dasatinib (year 2)	42,698			[16]
Cost of AT (year 1)	141,493			[4]
Monitoring and follow up (€)				
Costs of monitoring	3 months			
MMR/MR ^{4,5}	203			[4]
MR sub-optimal/intolerance	646			[4]
AP/BC	781	532	1,030	[4]
AT (subsequent years)	52	21	83	[4]
TFR	52	21	83	Assumed to be equal to AT (subsequent years)
Other costs (€)				
Cost of AEs				
Nilotinib	2,343	Attributed to the first year of treatment		[4]
Imatinib	2,343	Attributed to the first year of treatment		Assumed to be equal to nilotinib
Dasatinib	1,736	Attributed to the first year of treatment		[4]
Switch cost	4,922	Average cost of second-line treatments ¹ life time attributed to every patient switched		[4]
Cost of death due to disease	7,800			[4]

Table III. Mean annual costs

¹ Second-line treatments considered: dasatinib, ponatinib, bosutinib

AE = adverse events; MR^{4,5} = deep molecular response; MMR = major molecular response; MR = molecular response; AT = allogeneic transplantation; TFR = treatment-free remission

alternative scenario, considering the difference both in the annual spending and in the cumulative savings over the years.

In order to estimate the impact of the uncertainty of the input parameters on the results of the analysis, a one-way sensitivity analysis was conducted. In this analysis, some input data of the budget impact model were varied within an uncertainty range, and the impact on the final result was represented by a tornado graph.

In particular, the impact of the variation of the following parameters was analyzed:

1. Patients treated with nilotinib over time (min: 8% - max: 28%);
2. % of patients in acute chronic phase (min: 1% - max: 5%);
3. Relative risk (RR) of reaching MMR – dasatinib ($\pm 20\%$);
4. Probability of reaching MMR – nilotinib ($\pm 20\%$);
5. Probability of achieving TFR – nilotinib ($\pm 20\%$);

6. Monitoring cost (min-max as reported in Table III);

7. Other direct costs ($\pm 20\%$).

RESULTS

Below are the Budget Impact results in the perspective of the Italian National Health Service (NHS), over a time horizon from one to seven years from the start of treatment.

To date, the epidemiological model estimates 775 patients eligible for the treatment with the drugs in analysis. Table IV shows the evolution of patients over the different simulation years and within each Markovian state analyzed. The innovative scenario allows for a significant slowdown in the disease progression (-21.5% compared to the base case), as well as a lower number of therapeutic switches (-3%), and fewer deaths (-12.1%). In the alternative scenario, the number of patients in treatment who discontinue therapy without restarting is equal to 187.

	Patients distribution (n.)						
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7
Base case							
Treatment	488	485	482	479	476	474	471
Switch	268	271	274	277	280	282	285
Progression	7	6	6	5	5	4	4
Death	12	13	14	14	15	15	15
TFR	0	0	0	0	0	0	0
Total	775	775	775	775	775	775	775
Alternative scenario							
Treatment	496	493	491	372	353	323	294
Switch	262	265	268	271	273	275	277
Progression	5	5	4	4	4	3	3
Death	11	12	12	13	13	13	14
TFR	0	0	0	116	132	160	187
Total	775	775	775	775	775	775	775

Table IV. Patient distribution per analysis scenario and disease state
TFR = treatment-free remission

As a result of the effects on the health of the population, Figure 2 shows how the alternative scenario allows for an initial spending reduction of € 8.3 million in the first year, mainly due to the disinvestment generated by generic drugs. These annual spending reductions decrease to € 4.6 million in the third year of the analysis, rising again from the fourth year onwards, until reaching a spending reduction of over € 9.4 million in the seventh year of the analysis. In this case, the spending decrease is largely attributable to the greater

number of patients who can achieve the TFR. Figure 3 shows the evolution of the budget impact in cumulative terms. In particular, it is to be noted that the innovative strategy allows for a spending reduction at 4 years of approximately € 29 million, reaching over € 54 million at 7 years (30% and 36% of the total expenditure over 7 years in the base case, respectively). Finally, a one-way deterministic sensitivity analysis was performed, in which the spending differential between the two scenarios is

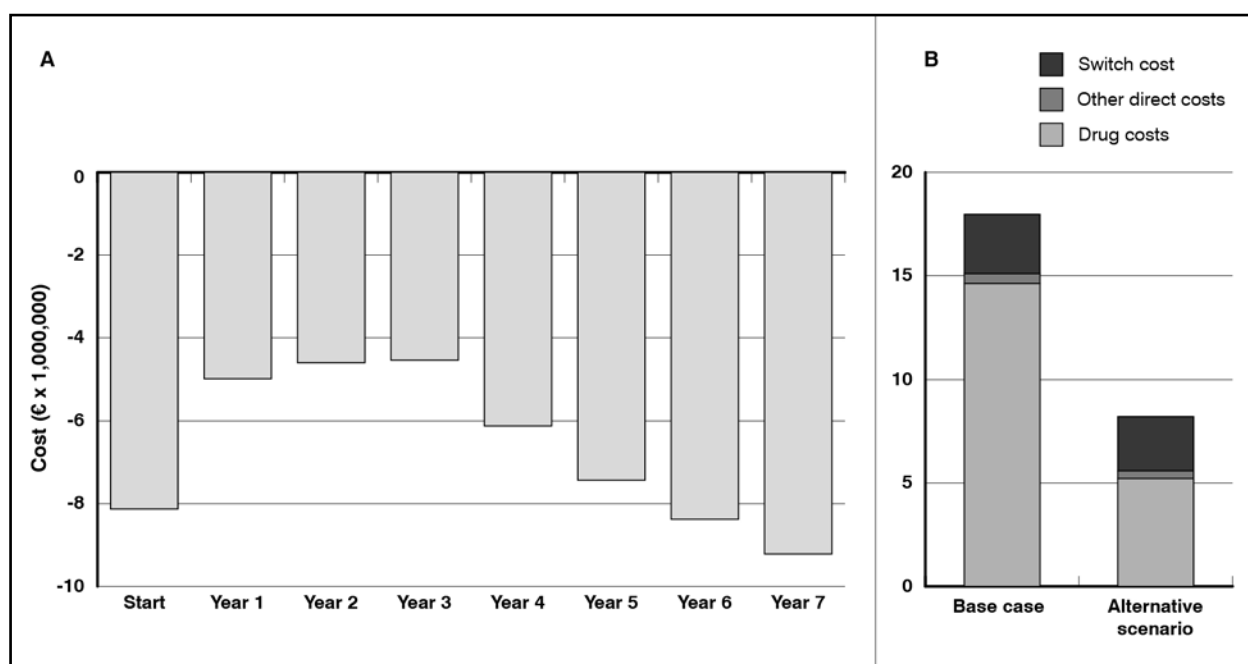


Figure 2. Results of the budget impact a) per year and b) at year 7: base case vs alternative scenario. Nilotinib: + 18%, imatinib (originator): -46%, dasatinib: -17%, imatinib (generic): +35%

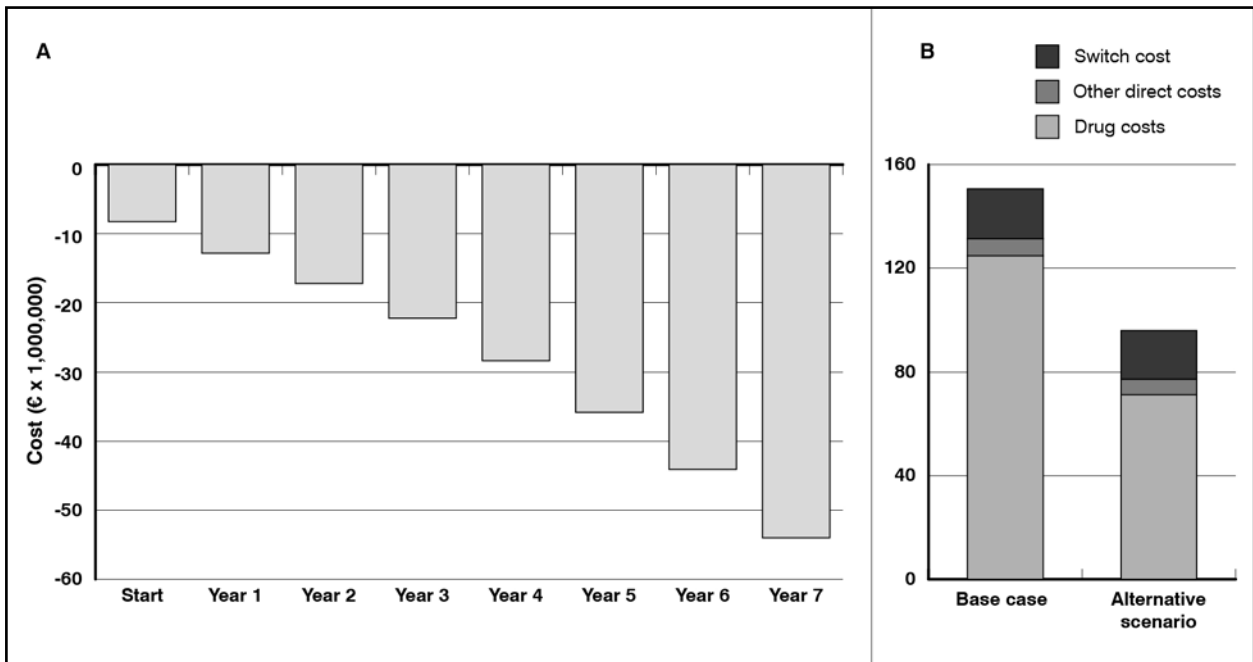


Figure 3. Results of the cumulative budget impact a) per year and b) at year 7: base case vs alternative scenario. Nilotinib: + 18%, imatinib (originator): -46% , dasatinib: -17%, imatinib (generic): +35%

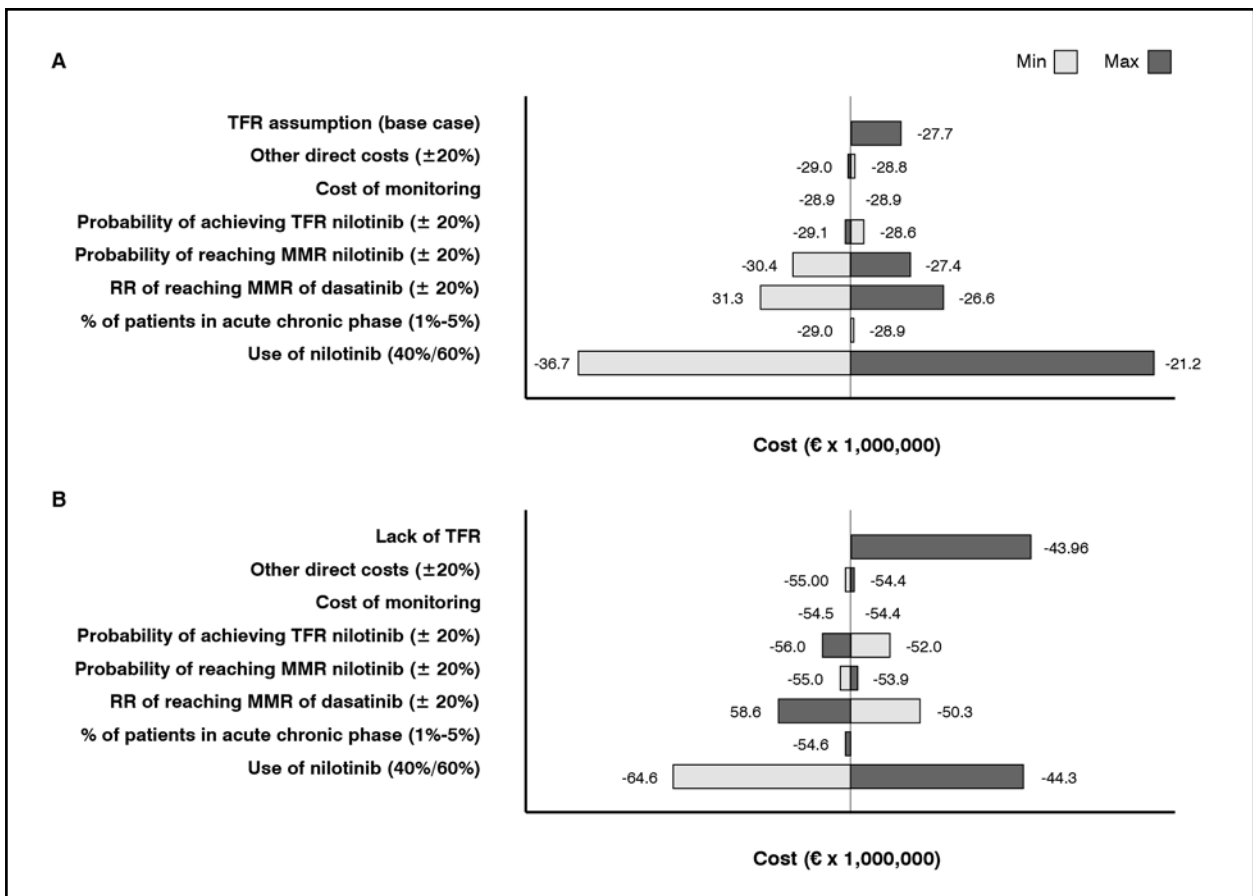


Figure 4. One-way sensitivity analysis at a) year 4 and b) at year 7 (million €)

reported, based on each modified parameter (Figure 4). The origin of the chart axis corresponds to the original differential of € 28.9 million at 4 years (Figure 4a) and € 54.5 million at 7 years (Figure 4b).

In all simulated scenarios, the innovative scenario always allows for a reduction in spending, versus an increase in nilotinib-treated patients. The main parameters that affect budget results are: a) the probability of reaching MMR with nilotinib; b) the probability of

reaching MMR with dasatinib; c) the market share absorbed by nilotinib. It is apparent that the initial molecular response is important not only for the patient's quality of life, but also in terms of potential savings. In addition, the sensitivity analysis shows that the growth in the use of nilotinib, together with the use of generic imatinib, could allow an increase in benefits proportional to the number of patients actually treated. Finally, the analysis shows that, shouldn't any TFR possibility exist, the reduction in spending would fall to € 27.7 million at 4 years and € 43.9 million in the seventh year of the analysis (+ € 1.2 and + € 10.5 million compared to the base case at 4 and 7 years, respectively).

DISCUSSION AND CONCLUSIONS

In recent clinical practice it has been shown that, after an adequate period of treatment and in the presence of a very deep and stable molecular response, TKI treatment can be safely discontinued, with good chance of success [7,19].

Numerous studies showed the efficacy of nilotinib in the first-line treatment of Philadelphia chromosome-positive chronic myeloid leukemia adult patients [6,19,20]. Besides these numerous advantages, obvious economic benefits can be identified, from the point of view of the National Health Service. However, in the Italian context, no work included an economic evaluation of nilotinib with regard to the treatment strategy with the possibility of TFR.

This Budget Impact model showed that the use of nilotinib, in conjunction with the introduction of the generic imatinib, represents on the one hand a significant response to the patient's medical needs and, on the other, generates at the same time an actual cost reduction, in the NHS's perspective.

The probability to achieve TFR could allow for significant spending reductions over time, which is a great tool for the decision-maker in order to maintain high levels of effectiveness and obtaining a decrease in the cost of therapies. The model estimated a net effect

of the TFR of over € 1.2 million at 4 years and € 10.5 million in the seventh year of the analysis, which is to be added to the effects generated by the spending reduction ensured by the patent expiration date of imatinib.

This work, like all the economic model, has various limits, that we attempted to control. First, the model was constructed by combining data from multiple randomized clinical trials that had homogeneous populations within the study, but heterogeneous ones among the studies considered. To date, the lack of sufficient information to provide an adequate meta-analysis and the inability to have appropriate comparative data did not allow for achieving better estimates. However, all clinical information and modeling assumptions have been validated and discussed with Key Opinion Leaders, who have identified adequate uncertainty parameters, which were then used to construct the deterministic sensitivity analysis.

Finally, it should be specified that in the model it was simulated that patients who fail therapy continue to remain within the model until the end of the 7 years of analysis, and at a constant therapy cost, estimated by national literature. This assumption is a methodological limit, which however has a little impact on the final estimates, since it represents a cost item constant for both the scenarios considered.

In conclusion, this paper verified the sustainability of the treatment with nilotinib compared to the main treatments currently used (dasatinib and imatinib originators). It has also been shown that the possibility to release resources by introducing the generic version of imatinib, in support of the nilotinib treatment, could be an effective strategy to generate additional savings and improve the patients' quality of life. Our study is a first attempt in Italy to quantify the potential cost savings generated by the therapeutic innovations of TKIs, as well as a useful tool which national and regional decision-makers could use to facilitate the allocative and management decisions concerning the specific resources for the treatment of newly diagnosed patients with Ph+ CML-CP.

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APPENDIX A

With the aim to model the natural history of adult patients with Ph+ CML-CP who undergone to first-line treatment with nilotinib, imatinib or dasatinib, it was necessary to make some assumptions. The clinical aspects of these assumptions have been reviewed and approved by Prof. Saglio.

1. Patients who remain in the TFR state for more than 1 year have a high probability to remain there also in the next years;
2. Patients who maintain MR^{4.5} and are not still ready, can go in the next years;
3. The right modeling of the switch state must be represented by the weighting of

patients who switch to dasatinib or bosutinib because of intolerance (2/3 of the patients) and patients who switch to ponatinib because of resistance (1/3 of the patients);

4. Death due to disease is only possible during advance states of illness (AP/BC);
5. The distribution of patients who maintain MR^{4.5} from 1 to 4 years is linear;
6. Values range of some parameters were provided to implement the sensitivity analysis.

Table IA shows the transition probability deriving from the assumptions above.

Probability	Nilotinib [6,20]	Imatinib [6]	Dasatinib [6,8]
From start of treatment to MMR	0.73	0.54	0.68
From start of treatment to sub-optimal response/intolerance	0.24	0.42	0.29
From start of treatment to AP/BC	0.02	0.04	0.03
To stay in MMR	0.11	0.13	0.12
From MMR to MMR ^{1*}	0.89	0.87	0.88
From MMR ¹ to MMR	0.12	0.15	0.20
From MMR ¹ to MMR ^{1.5*}	0.88	0.85	0.80
From MMR ^{1.5} to MMR	0.14	0.18	0.28
From MMR ^{1.5} to MMR ^{2*}	0.86	0.82	0.72
From MMR ² to MMR	0.16	0.22	0.35
From MMR ² to MMR ^{2.5*}	0.83	0.78	0.64
From MMR ^{2.5} to MMR	0.20	0.28	0.43
From MMR ^{2.5} to MMR ^{3*}	0.80	0.71	0.57
From MMR ³ to MMR	0.06	0.39	0.51
From MMR ³ to MMR ^{3.5*}	0.94	0.61	0.49
From MMR ^{3.5} to MMR	0.05	0.15	0.59
From MMR ^{3.5} to MMR ^{x*}	0.94	0.85	0.41
From MMR ^x to MMR	0.06	0.24	0.00
To stay in MMR ^x	0.06	0.24	1.00
From MMR ^x to MMR ^{0.5}	0.88	0.52	0.00
From STOP ^{0.5} to STOP ^x	0.48	0.44	0.00
From STOP ^{0.5} to STOP ¹	0.52	0.56	0.00
To stay in STOP ¹	0.95	0.95	0.00
From STOP ¹ to STOP ^x	0.05	0.05	0.00
From MMR to Switch	0.003	0.003	0.003
From sub-optimal response/intolerance to Switch	1.00	1.00	1.00
From AP/BC to Allogeneic Transplantation	0.03	0.60	0.37
From AP/BC to death due to disease [#]	0.67	0.10	0.33
From AP/BC to Switch	0.3	0.3	0.30
To survive after transplantation	0.60	0.60	0.60
To die after transplantation	0.40	0.40	0.40
To survive after transplantation (years after the first)	0.95	0.95	0.95
To die after transplantation (years after the first)	0.05	0.05	0.05

Table IA. Six-month transition probabilities

* Probabilities from MMR to MMR X were calculated assuming a linear trend of patients who leave from MMR and reach and maintain MMR^{4.5} from 4 years

[#] Probabilities of death from pivotal trials were converted into the ratio between deceased patients and deceased patients + patients in AP/BC state as estimated by pivotal trials (because of the assumption that only patients in advance states of illness can die)