Cost-effectiveness of imatinib since it's introduction as a first-line treatment in the Netherlands

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Introduction

- Chronic Myeloid Leukemia (CML) has a substantial effect on life expectancy. Until the development of the tyrosine-kinase inhibitor (TKI) imatinib, the life expectancy of CML patients on interferon alpha (standard of care [SoC] for first line treatment in 2003) was 5-7 years.[1] Imatinib extended this to a close to normal expectancy[1], but the price of imatinib raised societal questions at introduction.
- Several aspects have changed since the introduction of imatinib, including evidence on long-term effectiveness[2,3,4], costing manual and patent expiration.
- The aim of this study is to model the varying cost-effectiveness of imatinib versus interferon in the Netherlands taking above changing aspects into consideration.
- At three time points — 2003 (introduction of imatinib tablet), 2011 (introduction of second generation TKI's [2GTKI] in the CML guidelines: nilotinib and dasatinib)[5] and 2018 (including patent expiration in 2016 and additional usage of 2GTKI bosutinib and the 3GTKI ponatinib)[6] — and to calculate the break-even point.

Methods

- A Markov model was developed for each of the three years (2003, 2011, and 2018), containing the four main health states of the disease: chronic phase (CP), accelerated phase (AP), blast crisis (BC), and death. Patients could die from non-CML related mortality in every health state except for patients in the BC.
- Over a near-lifetime horizon (25 years in 2003 and 50 years in 2011 and 2018), a hypothetical cohort of 1,000 treatment-naïve CML patients was modelled progressing through the different health states (Figure 1). A cycle length of 3 months was used.
- Data on efficacy, costs and utilities were obtained from literature available in the respective years to evaluate the cost-effectiveness of imatinib compared to interferon.
- Analyses were performed form a payer perspective.
- In the univariate analyses, the robustness of the results was tested.
- The primary outcome of the analyses — the incremental cost-effectiveness ratio (ICER) — was compared to the Willingness-to-pay (WTP) threshold calculated for that year. A break-even point was calculated with the use of the cumulative incremental net monetary benefit.

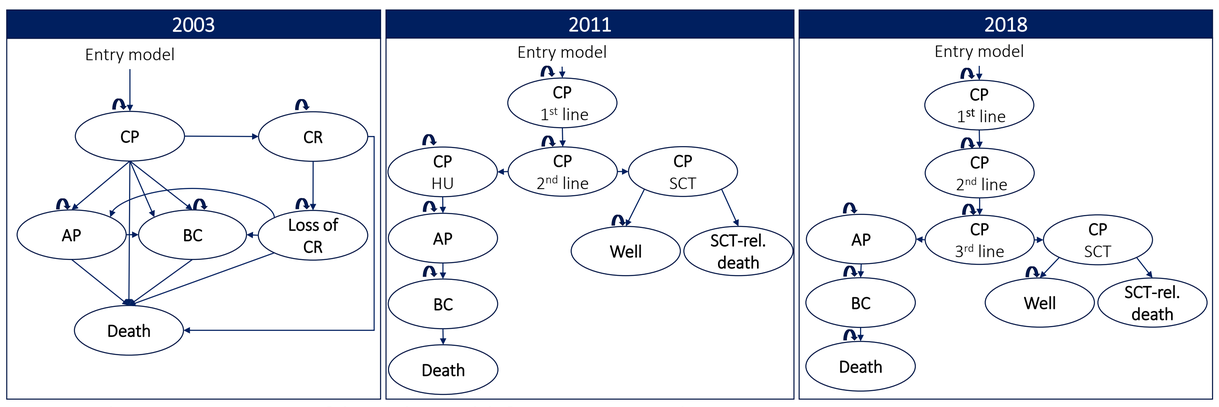

Figure 1. Schematic representation of the Markov models from 2003, 2011 and 2018.
Abbreviations: AP, accelerated phase; BC, blast crisis; CP, chronic phase; CR, cytogenetic response; HU, hydroxycarbamide; SCT, stem-cell transplantation; SCT-rel., stem-cell transplantation related.

Results

- The ICER calculated for 2003 was €17,878 and therefore not deemed cost-effective at the time of reimbursement.
- In 2011 and 2018, the ICER of €4,050 and €3,505 respectively were considered cost-effective. Several updated parameters resulted in a decrease in the ICER, while the WTP threshold increased in these years, resulting in a break-even point after 9 years (in 2012) (Figure 2).
- The tornado diagram (Figure 3) shows that the result of 2003 is not robust, due to the uncertainty of the utility of imatinib in the CP. The models are most sensitive to the dose intensities and the utilities of the TKIs.

Results (continue)

- Over the years, several parameters changed: In 2011, 2GTKI's were approved and the use of stem cell transplantation (SCT) in the CP was added. The discount rate for outcomes decrease from 4% to 1.5%.[7,8] In 2018, another 2GTKI and a 3GTKI were approved. These changes had the following impact on the ICER:
  - Discount rate drop: 27% decrease in the ICER
  - Approval of 2GTKI's: 38% decrease in the ICER
  - Use of SCT: 57% decrease in the ICER
  - Approval of another 2GTKI and 3GTKI: 2% decrease in the ICER.
  - Patent expiration: 23% decrease in the ICER.

Table 1. Results of the cost-effectiveness analysis of the three time points: 2003, 2011 and 2018.

Year	Incremental costs	Incremental QALYs	ICER
2003	€ 128,623,415	7,195	€ 17,878/QALY
2011	€ 88,863,394	21,884	€ 4,050/QALY
2018	€ 363,917,356	103,802	€ 3,505/QALY

Abbreviations: ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted Life-year.

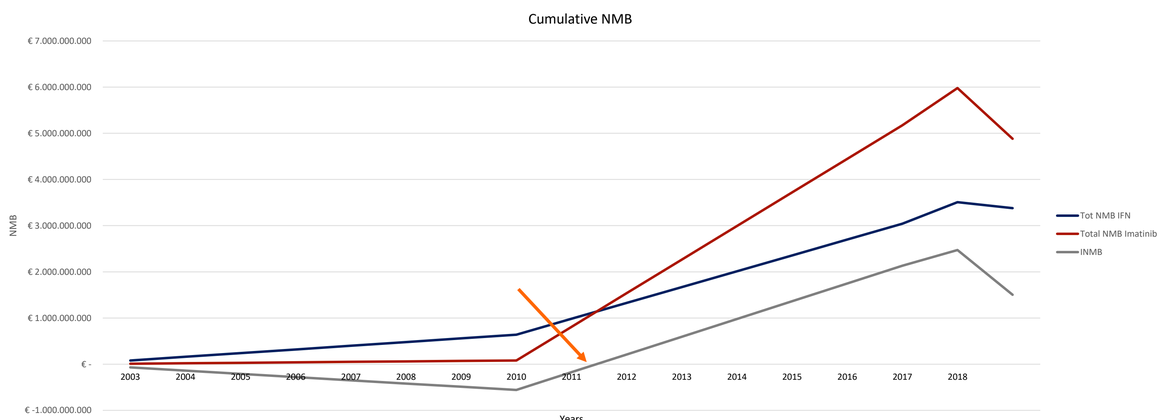

Figure 2. Societal break-even point: Cumulative incremental net monetary benefit.
Abbreviations: IFN, Interferon; INMB, incremental net monetary benefit; NMB, net monetary benefit.

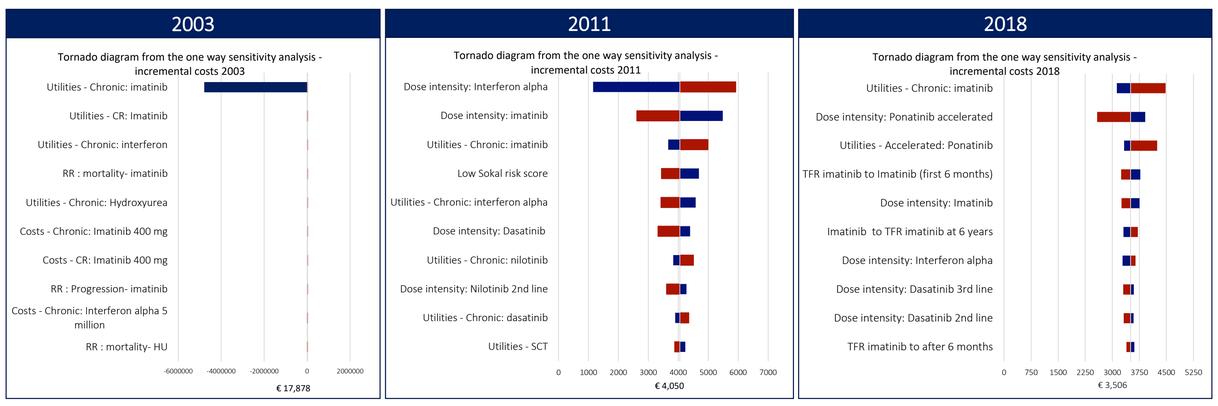

Figure 3. One way sensitivity analysis of the Markov models from 2003, 2011 and 2018.
Abbreviations: AP, accelerated phase; BC, blast crisis; CP, chronic phase; CR, cytogenetic response; HU, hydroxycarbamide; SCT, stem-cell transplantation; SCT-rel., stem-cell transplantation related.

Conclusion

- Though imatinib was not cost-effective as a first line treatment with an ICER of €17,878 in 2003, it became cost-effective in 2011 with an ICER of €4,050 and even more so in 2018 with an ICER of €3,505.
- This analysis shows that the ICER of a product can change over time. In the case of imatinib (the introduction of which raised societal questions on fairness), the ICER decreased over time, ultimately leading to a societal break-even point in 2012.
- A cost-effectiveness analysis should take patent expiration into account.

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