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Decision modelling using time on treatment data: evaluating the survival benefit of nilotinib versus imatinib in patients with chronic phase Ph+ CML

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INTRODUCTION

The ENESTnd randomised controlled trial demonstrated that nilotinib in newly diagnosed Philadelphia chromosome positive (Ph+) chronic phase chronic myeloid leukaemia (CML) has clinical superiority in terms of molecular and cytogenetic response over imatinib.[1,2] However the exact relationship between improvements in major molecular response (MMR), complete cytogenetic response (CCyR) and improvements in long-term survival is as yet unknown.

The objectives were:

1. to evaluate the survival benefit of first-line nilotinib compared to first-line imatinib for the treatment of Ph+ chronic phase CML.
2. to develop a decision analytic model which avoids the uncertainty of using surrogate response outcomes in economic evaluations.

Population: Adult patients with Ph+ CML diagnosed in chronic phase and who do not initially receive a stem cell transplant (SCT).

Intervention: Nilotinib 300 mg twice a day (b.i.d.)

Comparator: Imatinib 400 mg every day (q.d.)

Outcomes: Costs, life-years (LYs), quality-adjusted life-years (QALYs), incremental cost effectiveness ratios (ICERs).

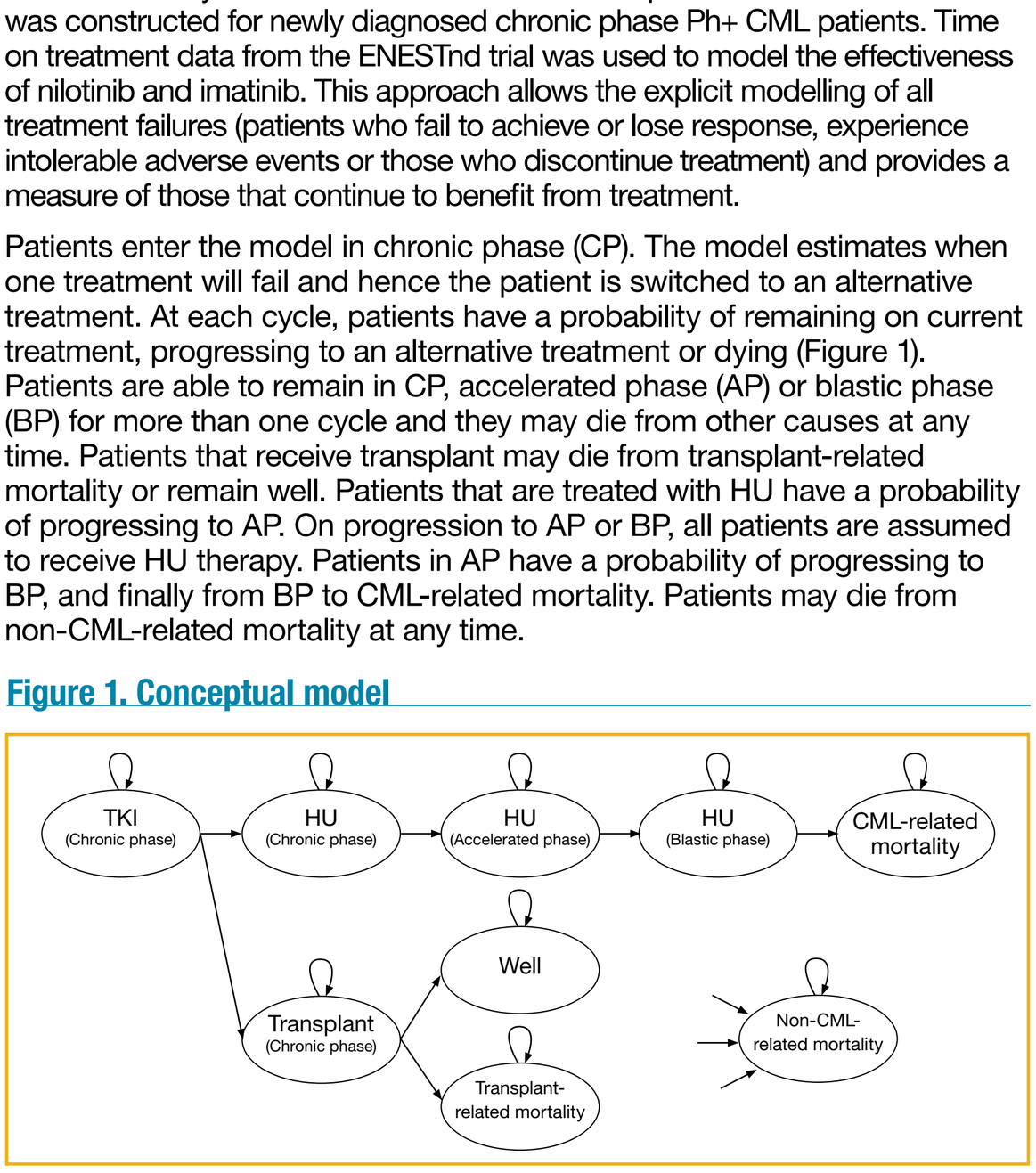
Perspective: UK National Health Service (NHS) and Personal Social Services (PSS).

MATERIALS AND METHODS

A decision analytic model of first-line nilotinib compared to first-line imatinib was constructed for newly diagnosed chronic phase Ph+ CML patients. Time on treatment data from the ENESTnd trial was used to model the effectiveness of nilotinib and imatinib. This approach allows the explicit modelling of all treatment failures (patients who fail to achieve or lose response, experience intolerable adverse events or those who discontinue treatment) and provides a measure of those that continue to benefit from treatment.

Patients enter the model in chronic phase (CP). The model estimates when one treatment will fail and hence the patient is switched to an alternative treatment. At each cycle, patients have a probability of remaining on current treatment, progressing to an alternative treatment or dying (Figure 1). Patients are able to remain in CP, accelerated phase (AP) or blastic phase (BP) for more than one cycle and they may die from other causes at any time. Patients that receive transplant may die from transplant-related mortality or remain well. Patients that are treated with HU have a probability of progressing to AP. On progression to AP or BP, all patients are assumed to receive HU therapy. Patients in AP have a probability of progressing to BP, and finally from BP to CML-related mortality. Patients may die from non-CML-related mortality at any time.

Figure 1. Conceptual model

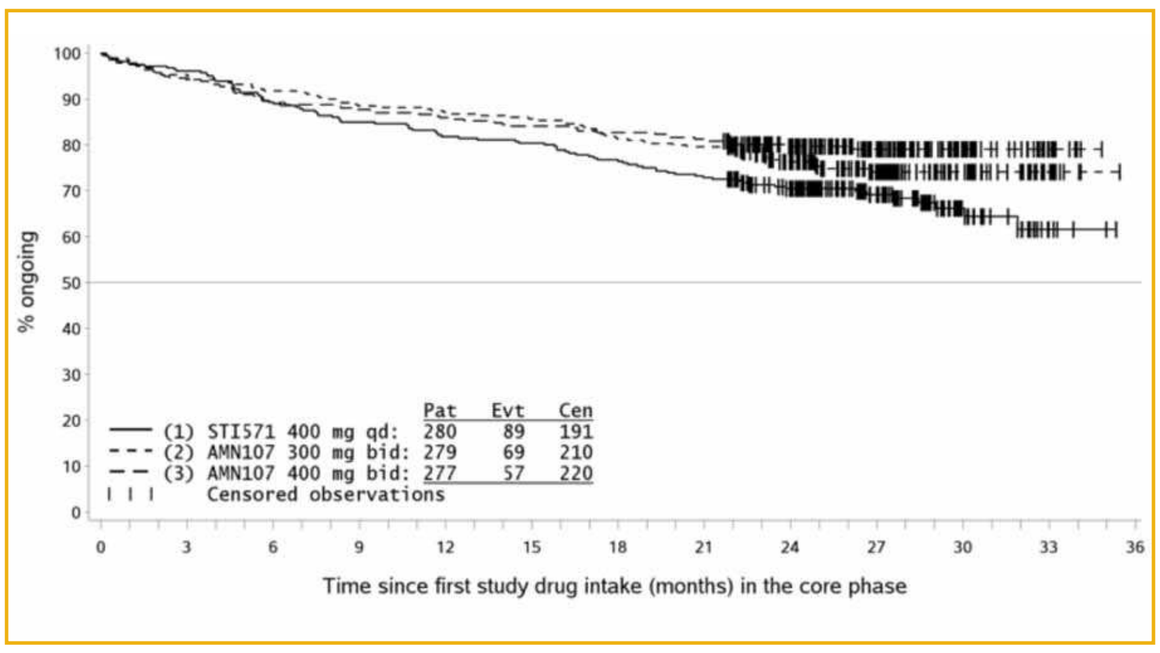


TKI = tyrosine kinase inhibitor. Nilotinib and Imatinib are TKIs.

Survival Estimates: The clinical effectiveness of first-line treatment was modelled using time on treatment data from the ENESTnd trial. This approach allows the explicit modelling of all treatment failures (patients who fail to achieve or lose response, experience intolerable adverse events, or those who discontinue treatment for other reasons) and directly reflects the costs associated with being on treatment.

In order to model time on treatment over the long term, a Weibull curve was fitted using regression analysis to a Kaplan-Meier curve of time on treatment from the ENESTnd trial based upon the numbers at risk and the numbers of events within the nilotinib arm (300 mg b.i.d.) and the imatinib arm (400 mg q.d.) (Figure 2). This method appropriately characterises the uncertainty in the data by fitting the curve more closely to data points with large numbers at risk and less censoring.

Figure 2. Kaplan-Meier estimate of time on treatment for ENESTnd trial 24 month primary analyses. STI571 = imatinib; AMN107 = nilotinib



Costs: Costs (Sterling, 2011) associated with the different drug therapies, stem cell transplantation, routine hospital appointments for administration and monitoring, and treatment for severe adverse events were included (Table I). A patient access scheme is available for first-line nilotinib therapy and was included in the analysis.

Utilities: EQ-5D utilities were applied to patients in each health state (Figure 1) and utility decrements were estimated for patients experiencing severe (grade 3 and 4) adverse events on TKI therapy (Table I).

Table I. Treatment costs, utilities and disutilities included in the model

Parameter	Value	Source
Costs		
Nilotinib 300 mg (28 days)	£2,432.85	[3]
Imatinib 400 mg (30 days)	£1,724.39	[4]
HU 500mg (25 days)	£10.47	[4]
Allogeneic SCT	£99,224.38	[5,6]
Utilities		
Chronic phase utility	0.854	[7]
Accelerated phase utility	0.595	[7]
Blastic phase utility	0.595	[7]
Transplant utility	0.813	Calculated*
Disutilities		
Nilotinib disutility	0.010	Calculated*
Imatinib disutility	0.016	Calculated*
HU disutility	0	Assumption

*Based on the frequency and duration of serious adverse events. HU = hydroxyurea; SCT = stem cell transplantation.

RESULTS

The mean undiscounted survival was estimated to be 11.80 years in the nilotinib arm compared to 10.44 years in the imatinib arm; a difference of 1.36 LYs (Table II). Using a discounting rate of 3.5%, patients are estimate to accrue an additional 0.88 LYs in the nilotinib arm compared to the imatinib arm. After adjusting for quality of life, patients are estimated to gain an additional 0.70 QALYs (discounted) in the nilotinib arm compared to the imatinib arm at a cost per QALY gained of £4,500 (discounted).

Table II. Cost-effectiveness results from the probabilistic sensitivity analysis (PSA)

Parameter	LYs	QALYs	Lifetime costs
Undiscounted			
Nilotinib	11.80	9.02	£213,500
Imatinib	10.44	7.97	£202,700
Difference	1.36	1.06	£10,800
ICER	£8,000	£10,300	
Discounted			
Nilotinib	8.98	6.95	£174,200
Imatinib	8.09	6.25	£171,100
Difference	0.88	0.70	£3,100
ICER	£3,600	£4,500	

Costs rounded to nearest hundred. ICER = incremental cost-effectiveness ratio; LYs = life-years; QALYs = quality-adjusted life-years.

CONCLUSIONS

- **The results suggest that nilotinib produces substantially greater long-term survival and QALY gains than treatment with imatinib.**
- **The health benefits of nilotinib can be achieved at a marginal incremental cost which is well below a cost-effectiveness threshold of £20,000 per QALY gained.**
- **The use of time on treatment data avoids the need for surrogate response outcomes and their associated uncertainty.**

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