BACKGROUND

- Gastrointestinal stromal tumours (GISTs) are the most common form of gastrointestinal mesenchymal tumour [1].
- The age-standardized incidence rates of GIST are typically between 0.5 and 1.2 per 100,000 person-years for national and global populations [2-4]. However, this is further reduced in our target population of patients who have progressive disease. The mortality rate has been shown to be as high as 80% during a follow-up period of 74 months for malignant GIST [5,6].
- Regorafenib is an oral multikinase inhibitor that blocks the activity of multiple protein kinases involved in tumour angiogenesis, oncogenes, and the tumour microenvironment [5,6].
- Regorafenib is approved for the treatment of unresectable or metastatic GIST in patients who progressed on, or intolerant to, prior treatment with imatinib and sunitinib [5,7].
- The phase III, double-blind, placebo-controlled CORDIS trial (n=199) showed that regorafenib plus best supportive care (BSC) improved the primary endpoint of progression-free survival (PFS) versus placebo plus BSC in patients with advanced GIST who had progressed during treatment with at least imatinib and sunitinib.

OBJECTIVES

- To evaluate the cost-effectiveness of regorafenib compared with placebo for patients receiving treatment for unresectable or metastatic GIST after failure/intolerance to imatinib and sunitinib in an English setting.

METHODS

- Using patient level data, a partitioned survival model was developed with three main health states: progression-free (on or off treatment), progressed, and dead (see figure 2). The perspective of the English NHS was taken.
- The model compared regorafenib and BSC (hereafter called the regorafenib arm) versus placebo and BSC (hereafter known as the placebo arm).
- Due to the crossover design of the trial, a significant proportion of patients crossed from the placebo arm to the treatment arm (88%, n=566/66) following disease progression. Crossover bias was corrected using accelerated failure time models; Iterative Parameter Estimation (IPE) and Rank Preserving Structural Failure Time (RPSFT), with stratification and reestimation to reduce bias as per Latimer 2012 [8]. The hazard ratio (HR) determining the use of the RPSFT method was 0.54 (95% CI 0.29-1.01, p=0.03); HR determined using the IPE method was 0.37 (95% CI 0.30-1.06, p=0.04). See figure 2 for the Kaplan-Meier plots of effectiveness using the IPE and RPSFT adjustment methods.
- IPE crossover was chosen as the base case since Morden’s study of 1,000-simulated datasets showed that this method performed particularly well in terms of reducing bias in the estimates of the true treatment effect [9]. Hazard ratios for IPE and RPSFT methods were estimated using a Weibull model and a logrank test, respectively. The Inverse Probability of Censoring Weights (IPCW) method for crossover adjustment was also explored, however implausible results were generated due to the very high level of crossover.
- PFS and OS estimates for regorafenib were derived directly from the trial data. Parametric extrapolations of the data using Exponential, Gompertz, Loglogistic, Lognormal and Weibull functions were fitted so that the model used fully parametric functions for its PFS and OS estimates. The Loglogistic function was applied as it generated the lowest Akaike Information Criterion (AIC). The other parametric models were tested in the one-way sensitivity analysis (OWSA).
- Resource use was determined from a physician survey of 15 GIST medical oncologists in England and Wales, and was deemed suitable for inclusion in the model by a further two medical oncologists. Unit costs were obtained from 2014-15 NHS resource costs and the BNF 71 (March 2016)[11].
- EQ-5D-5L was used as the measure of quality of life based on data collected during the CORDIS trial. Two methods were used to generate health state utilities: a anchor-based conjoint and a repeated measures analysis. The paired-samples comparison was chosen over the repeated measured analysis in the base case to reduce measurement bias. Both regorafenib and placebo arms were assumed to have the same utility value in the progression free state as there was no statistically significant effect due to treatment arm on the utility value within the progression free state. The paired samples comparison yielded a utility of 0.767 (SE 0.025) for the placebo state and 0.647 (SE 0.031) for the progressed state.

RESULTS

- In the base case, regorafenib treatment provided an additional 1.047 life years, 0.748 QALYs and 0.708 progression-free life years over BSC, per patient over a lifetime horizon. The additional per patient drug acquisition cost of regorafenib compared to placebo was £24,592, and incremental total cost was £23,114 per placebo. The price of regorafenib reflects a confidential price with an applied discount. This implies ICER of £34,430 per QALY gained, per patient.
- Table 2 lists the impact of crossover adjustment in the ICER estimates. Adjustment using IPE and RPSFT methods gave similar ICERs; £34,420 and £40,188 per QALY gained, respectively. This difference can be largely attributed to the incremental gain in life years predicted by each method, IPE and RPSFT predicting an incremental gain of 1.047 and 0.876 years, respectively.

Sensitivity analyses

- One-way sensitivity analyses were performed on key model inputs; figure 3 shows a tornado diagram of the top 10 model drivers. The model was most sensitive to a time horizon of 5 years and the choice of parametric model used to extrapolate GRID overall survival data.
- PSA was also performed. Simulations with 3,000 iterations produced the cost-effectiveness plane shown in figure 4. Average results of the PSA, using IPE as a base case, revealed the average incremental life years gained was 1.038, incremental QALYs gained was 0.744, incremental costs were £26,358 and the ICER was £33,358 per QALY gained, per patient vs BSC. Results from the PSA were consistent with the base case.
- Figure 5 shows the cost-effectiveness acceptability curve (using QALYs). At a willingness-to-pay threshold of £50,000 per QALY gained, regorafenib has an 81% probability of cost-effectiveness.

CONCLUSIONS

- In this trial with frequent and early crossover, statistical correction made a substantial difference to modelled cost-effectiveness. Failing to apply appropriate correction for crossover lead to unreliable outcomes and ICER estimates.
- Regorafenib was found to be a cost-effective treatment for patients with metastatic/unresectable GIST after treatment failure/intolerance with imatinib and sunitinib.
- Sensitivity analysis revealed that crossover adjustment provided the most variation in the ICER estimate, and therefore was an important inclusion into the model.

REFERENCES