Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The aim was to quantify the cost-benefit of sorafenib as a new addition to therapy before liver transplant, compared with no bridging therapy, for patients with hepatocellular carcinoma. The authors concluded that sorafenib was cost-effective, particularly when the median time to liver transplant was less than six months, but more research was required on its safety profile before transplantation. The methods and results were generally reported poorly and the conclusions should be considered with caution.

Type of economic evaluation
Cost-utility analysis, cost-benefit analysis

Study objective
The aim was to quantify the cost-benefit of sorafenib as a new addition to therapy before a liver transplant, compared with no bridging therapy, for patients with T2 tumour hepatocellular carcinoma, with compensated cirrhosis, who met the Milan criteria for transplant eligibility.

Interventions
Sorafenib, three capsules per day, was compared with no bridging therapy, for the first six months on the waiting list for a transplant. Sorafenib was administered until cancer progressed or decompensated cirrhosis developed. The dose was based on 80% of patients receiving the recommended four capsules per day. Patients who did not receive bridging therapy could receive sorafenib after they were removed from the waiting list.

Location/setting
Italy/secondary care.

Methods
Analytical approach:
A Markov model with a one-day cycle length was used to synthesise the data from a variety of sources. The health states were: with compensated cirrhosis, with decompensated cirrhosis, liver transplant, after liver transplant follow-up, drop-out from waiting list with Barcelona Clinic Liver Cancer (BCLC) stages B, C, or D, and death. The time horizon was 10 years and the authors stated that a payer's perspective was adopted.

Effectiveness data:
The hazard ratio for the time to hepatocellular carcinoma progression for patients on sorafenib was estimated to be 0.47 based on a published subgroup analysis of the efficacy of sorafenib for intermediate hepatocellular carcinomas. The probability of leaving the waiting list each month with no bridging therapy came from three published studies, and was modified linearly by the sorafenib hazard ratio to produce the estimate for patients on sorafenib.

Monetary benefit and utility valuations:
The utilities for before and after transplant were from a published systematic review.

Measure of benefit:
The primary measure of benefit was quality-adjusted life-days (QALDs). The probability of a liver transplant and the net health benefit were reported. The benefits were discounted at a rate of 3% per annum.
Cost data:
The direct health-related costs included: sorafenib therapy, follow-up care, and liver transplantation. These costs were the payments at the time from the Italian public health care system, based on the authors' hospital. The median treatment duration and survival times, with sorafenib, were from the SHARP trial. The price year was 2008 and all costs were reported in Euros (EUR). They were discounted at rate of 3% per annum.

Analysis of uncertainty:
One-way sensitivity analysis was performed on all variables. A two-way sensitivity analysis was performed on the sorafenib hazard rate and the median time to liver transplant. Probabilistic sensitivity analysis was performed, with beta distributions for all variables. A scenario was considered with the potential introduction of locoregional therapies for patients who did not receive bridging therapy, after six months on the waiting list; one percutaneous ablation and one transarterial chemoembolisation.

Results
In the base case, the percentage of patients receiving a transplant was 52% with sorafenib, and 47% with no bridging therapy. The rate of death was 48% with sorafenib and 53% with no bridging therapy, producing a gain of 89 QALDs per patient treated.

The probabilistic sensitivity analysis showed that the expected QALDs per patient were 1,350 with sorafenib (80% CI 1,151 to 1,434), compared with 1,244 with no bridging therapy (80% CI 978 to 1,368); The median survival benefit with sorafenib, compared with no therapy, was 94 QALDs (80% CI 38 to 210).

Compared with no bridging therapy, sorafenib resulted in an incremental cost-utility ratio of EUR 197 per QALD gained and an incremental net health benefit of 37 QALDs, at a willingness-to-pay threshold of EUR 346 per QALD.

One-way sensitivity analysis showed that the results were most sensitive to variations in the hazard ratio and the median time to liver transplant. The threshold value for the hazard ratio, where sorafenib no longer produced a net health benefit, was 0.75. The threshold value for the median time to liver transplant was two years.

Two-way sensitivity analysis revealed an almost linear relationship between the sorafenib hazard ratio and the transplant probability ratio, which was a proxy for transplant prioritisation. The net health benefit fell when locoregional therapies were introduced for patients who did not receive bridging therapy, after six months on the waiting list.

Authors' conclusions
The authors concluded that sorafenib was cost-effective compared with no bridging therapy for T2 hepatocellular carcinoma patients awaiting liver transplant, particularly when the median time to transplant was less than six months. More research was required on the safety profile of sorafenib before transplantation.

CRD commentary
Interventions:
The interventions were well described, except that the dose of sorafenib was not reported, and they appear to have been relevant for the secondary health care setting. The use of other therapies in the first six months on the waiting list was not considered and this treatment assumption might not be appropriate in other settings.

Effectiveness/benefits:
The estimate of sorafenib efficacy was reported, but its confidence interval was not. The estimate appears to have been from a subgroup analysis of data from a randomised controlled trial (the SHARP trial); the details of this trial and the subgroup analysis were not clearly reported. Particularly, whether the subgroup analysis was pre-specified and whether patients received three doses per day in this subgroup or not. There was no indication that a systematic review was conducted, making it unclear whether all the relevant sources of efficacy were identified. The hazard ratio was used to convert the probability of drop-out from the waiting list per month, but it was unclear if the method was appropriate or if others might have been better. The health state utilities were from a published systematic review, which was not described and neither were the sources used. The method used to estimate the willingness to pay was described, but no sensitivity analysis was conducted on this estimate. The analysis excluded adverse events, as these had not been
established.

Costs:
The cost categories were relevant to the perspective taken. The resource use was not reported for many items, such as the number and type of physician follow-up visits, which limits the generalisability of the results. The sources of the unit costs were not given in detail. The authors did not report any adjustments to these costs.

Analysis and results:
The analytic approach was appropriate and a diagram of the Markov model was provided. It was noted that the model was designed while awaiting robust data on the safety of sorafenib. The reported calculations for the incremental cost-utility ratio and the incremental net benefit ratio appear to have been incorrect, as they did not seem to use the differences in costs and benefits between the two treatments. The total costs for each strategy were not reported and, in the base case, only the incremental QALDs were provided. The sensitivity of the model to all variables was not reported. It would have been more informative to present the results of the probabilistic sensitivity analysis in a cost-effectiveness acceptability curve. The authors discussed some of the limitations of their analysis, including the potential negative (angiogenesis inhibiting) effect of sorafenib on the surgery outcome and the need for clinical trials to provide data on this. They highlighted that their results should be considered with caution.

Concluding remarks:
The methods and results were generally reported poorly and the conclusions should be considered with caution.

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