Use of Sorafenib in Patients With Hepatocellular Carcinoma Before Liver Transplantation: A Cost-Benefit Analysis While Awaiting Data on Sorafenib Safety

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The role of bridging therapies for patients with hepatocellular carcinoma (HCC) on the waiting list for liver transplantation (LT) remains controversial. There is strong evidence to support the effectiveness of sorafenib in extending the time to progression of HCC. Using a Markov model, we compared two strategies: one using sorafenib as neoadjuvant therapy before LT (Strategy A), and the other using no bridging therapy in the first 6 months (Strategy B). Reference case: T2 HCC patient with compensated cirrhosis. The benefit of sorafenib in delaying time to HCC progression was expressed as the hazard ratio (HR) and taken from recently published randomized trials. The endpoints considered were: survival benefit measured in quality-adjusted life days (QALDs), transplant probability, costs (C) in €, willingness to pay (WTP), and net health benefit (NHB), where NHB = survival benefit − C/WTP. The calculated WTP of sorafenib in Italy was 346 € per QALD. Probabilistic sensitivity analysis showed a median survival benefit of 94 QALDs (10% percentile = 38, 90% percentile = 210). In the base-case scenario (HR = 0.47, monthly dropout probability = 5%, median time to LT = 3 months), the gain in LT probability due to sorafenib was 5% and it increased proportionally with increasing median times to LT and decreasing HR. In the cost-benefit analysis, the incremental NHB of Strategy A versus Strategy B was 37 QALDs; it increased as sorafenib HR decreased and when median times to LT were shorter than 6 months, whereas for longer times it gradually dropped, particularly when Strategy B included effective locoregional treatments. *Conclusion:* Sorafenib neoadjuvant therapy is cost-effective by comparison with no therapy for T2-HCC patients waiting for LT, particularly for median times to LT under 6 months. (HEPATOLOGY 2010;51:165-173.)

Due to the disparity between organ availability and demand, dropout while on the waiting list (WL) has become the main predictor of survival for adult patients awaiting liver transplantation (LT) for malignant or nonmalignant (NM) chronic liver disease when an inten-tion-to-treat analysis is applied.[1-3] Tumor progression before LT was the main reason for removing patients with hepatocellular carcinoma (HCC) meeting the Milan criteria (MC)[4] from the WL, whereas for NM patients the main reason was the patient's death due to complicated cirrhosis.[3,5]

A first way to contain this considerable dropout risk is to proportionally increase the probability of transplantation for patients with more severe liver disease by adopting specific prioritization policies. This is the primary strategy used by the US liver allocation system, which has adopted the model for endstage liver disease (MELD) in recent years to establish which HCC and non-HCC patients take priority for transplantation.[6]

For HCC patients, the dropout risk might also be reduced by treating the tumor in order to slow its progression. Locoregional treatments, such as resection, ablation (percutaneous or laparoscopic), and transarterial chemoembolization (TACE) have been proposed as neoadjuvant therapies before LT.[7-9]

Although these procedures have a well-established efficacy in prolonging the survival of HCC patients,[10] no studies strongly support and exactly measure their effectiveness in reducing the risk of dropout among HCC patient candidates for LT.[11] This is the main reason why

*In Strategy A, Sorafenib was used only in patients with compensated cirrhosis during the waiting list
**In Strategy B, Sorafenib was used only in BCLC C patients with compensated cirrhosis after dropout.

Fig. 1. The event pathway: decision tree and states of health.

recent guidelines have prudently suggested that locoregional bridging therapies "can be considered" only if the median time on the WL exceeds 6 months.[10]

A new systemic, molecularly targeted therapy, sorafenib, was recently tested in two large Phase 3 randomized clinical trials (RCTs), showing a significant efficacy in delaying tumor progression[12,13] in patients with intermediate-advanced HCC. This effect was maintained in demographically different study populations, as demonstrated by the similar hazard ratios (HRs) in the two RCTs. Unlike the case of locoregional therapies, therefore, the efficacy of sorafenib in slowing tumor progression has been demonstrated and quantified with the highest level of scientific evidence. On the other hand, such a powerful antiangiogenic effect as that of sorafenib may interfere with vessel repair and thus give rise to a potentially higher risk of postsurgical complications, especially in the case of unscheduled measures such as transplantation. There are no data, however, to demonstrate and measure this potential toxicity of sorafenib in surgical patients.

In the present study, we hypothesized that by delaying tumor progression sorafenib could decrease dropout from the transplant WL and thus increase the number of patients able to be transplanted. We developed a Markov model to represent and quantify the potential cost-benefit ratio of sorafenib as a neoadjuvant therapy for HCC patients meeting the MC and awaiting LT. It has to be emphasized, however, that this model was designed while awaiting robust data on the safety of sorafenib.

Patients and Methods

Definitions and Endpoints. The study focused on HCC candidates for LT meeting the MC (Fig. 1). As a reference case, our model considered a patient with compensated cirrhosis[14] and a T2 tumor,[15] i.e., one nodule 2-5 cm or 2-3 nodules ≤3 cm. The effect of a generic neoadjuvant therapy on time to progression was expressed in our model in terms of HR, as in recent RCTs.[12,13] In the particular context of the WL before LT, we considered this HR value as a linear factor for correcting the conventional dropout probability (DP) of HCC patients awaiting LT. Thus, for example, if the monthly conventional DP for HCC patients was 4% and the treatment HR was 0.50, then their treatment-modified dropout probability (SDP) became 4% * 0.50 = 2% according to the following formula: SDP = HR * DP.

Although there are no robust studies measuring the efficacy of locoregional therapies in terms of reducing the risk of dropout, because we know the exact HR of sorafenib in extending the time to progression of HCC the aim of this study was to compare two strategies: one using sorafenib as a neoadjuvant therapy before LT (Strategy A), and one with no bridging therapies (Strategy B). In current clinical practice, however, patients likely to have to wait some time and not given priority are treated almost everywhere. For this reason our model also included a specific sensitivity analysis considering the potential introduction of locoregional therapies in Strategy B patients when their median time on the WL exceeded 6 months.

Starting from these assumptions, we considered four endpoints to quantify the potential benefits of sorafenib neoadjuvant therapy:

1. Gain in transplant probability. The main assumption of this study is that, by delaying tumor progression, sorafenib could decrease dropout from the transplant WL and thus increase the number of patients able to be transplanted.

2. Survival benefit. The utility of each strategy was measured in terms of quality-adjusted intention-to-treat survival and this was expressed in quality-adjusted life days (QALDs). We also measured the proportional decrease in transplant priority for Strategy A patients that was needed to balance the utility of the two strategies.

3. Marginal cost-utility ratio. We considered as fundamental cost-utility outcome measure the ratio between costs and QALDs, characterizing each strategy in each particular scenario. The difference between these calculated values (Strategy A cost/utility − Strategy B cost/utility) was the marginal cost-utility ratio.

4. Incremental net health benefit (NHB). The NHB of an alternative treatment is calculated using the formula (16): NHB = U − C / WTP, where U is the utility, C is the cost, and WTP is the willingness to pay. WTP is represented by the ratio of the mean incremental cost to the mean incremental effectiveness (utility). In the

Table 1. Variables Used to Construct the Model

Variables	Base-Case Analysis	Range Tested	Source
PRETRANSPLANT VARIABLES			
Median time to transplant (days) HCC (meeting Milan)	90	32–145	(6, 21)
Dropout probability for HCC progression per month	5%	4–6%	(17–19)
Sorafenib hazard ratio for tumor progression	0.47	0.23–0.93	(23)
Compensated cirrhosis (2-year survival rate)	90%	70–100%	(14)
Decompensated cirrhosis (2-year survival rate)	50%	40%–60%	(14)
Annual probability of transition from compensated to decompensated	0.07	0.05–0.10	(14)
Treated BCLC stage B median survival (months)	20	19–21	(24,25)
Treated BCLC stage C median survival (months)	10	9–11	(24,25)
Untreated BCLC stage C median survival	7	6–8	(24, 25)
BCLC stage D median survival (months)	4	3–5	(24, 25)
Pretransplant quality-of-life utility	0.53	0.45–0.6	(21)
POSTTRANSPLANT VARIABLES			
Transplant-related operative death	5%	2–8%	(21)
Posttransplant survival (probability/5 years)	72%	70–75%	(21)
Posttransplant quality-of-life utility	0.62	0.61–0.63	(21)
VARIABLES FOR COST ANALYSIS			
Follow-up while awaiting LT (€/day)	100	70–120	N/A
Sorafenib while awaiting LT (€/day)	150	100–200	N/A
Percutaneous ablation (€)	7000	6000–8000	N/A
Chemo-embolization (€)	3300	3000–4000	N/A
Sorafenib after dropout (€/day)	150	100–200	N/A
Follow-up after dropout (€/day)	120	90–150	N/A
Transplantation (€)	80000	60000–100000	N/A
Follow-up therapy after transplantation (€/day)	50	40–60	N/A
VARIABLES FOR CALCULATING WTP IN ITALY			
Cost of each Sorafenib capsule (€)	50	N/A	N/A
Median duration of treatment (months)	5.3	0.2–16.1	(12)
Proportion receiving more than 80% of daily dose	76%	N/A	(12)
Sorafenib group median survival (months)	10.7	N/A	(12)
Placebo group median survival (months)	7.9	N/A	(12)
Time horizon (years)	10	5–15	N/A

Abbreviations: HCC, hepatocellular carcinoma; BCLC, Barcelona Clinic Liver Cancer; WL, waiting list; LT, liver transplantation; WTP, willingness to pay.

present study the WTP was defined as the cost per QALD gained that society has already accepted as being cost-effective for a patient treated with sorafenib. Given a particular WTP value, the difference between the NHBs of the two strategies is defined as the "incremental NHB."

Model Assumptions and Variables. We constructed a Markov model, which examines the decision whether or not to use sorafenib as neoadjuvant therapy before LT.

We hypothesized that therapy with sorafenib started at the time of listing. Moreover, as in the Sharp trial and in Italian clinical practice, therapy with sorafenib was stopped once patients have tumor progression. Thus, Strategy A had the potential benefits of sorafenib therapy only during the WL (and not after dropout), whereas Strategy B benefited from sorafenib therapy only after dropout from the WL in patients with advanced HCC and compensated cirrhosis. Moreover, our model takes into account the risk of decompensation in patients with compensated cirrhosis.[13] We assumed that sorafenib therapy was administered only to patients with a compensated cirrhosis.

In constructing the model, we made several assumptions based on data available in the literature[17-24] or justifiable clinical opinions (Table 1).

WL Variables. The dropout probability from the WL of our reference HCC case receiving no bridging therapies (Strategy B) was calculated from four major studies,[17-20] and this probability was confirmed in recent data from the UNOS database,[6,21,22] where only a minority of patients had locoregional bridging therapies and the median time to LT was relatively short. The median time to transplant was used, rather than the median time on the WL, to calculate the daily probability of getting a transplant, as in other recent models,[21,22] because the latter excludes the time spent on the list with an inactive status.

As mentioned above, we assumed that the conventional dropout probability of HCC patients was modified linearly by the specific sorafenib HR on time to progression.[11,12] In the base-case scenario, we assumed an HR = 0.47, which is the value obtained in subgroup analyses on the efficacy of sorafenib for intermediate HCCs.[23]

Because there are no robust data in the literature on the tumor stage of WL patients at the moment of dropout, in our model we assumed that patients with compensated cirrhosis removed from the WL due to tumor progression were Barcelona clinic liver cancer (BCLC) B and C patients in equal proportions, whereas those with decompensated cirrhosis and tumor progression were assumed to be in BCLC D stage. According to recently published guidelines,[24,25] patients with compensated cirrhosis and a tumor progressing beyond the MC (BCLC B and C patients) should be treated with chemoembolization (standard care for BCLC B patients) or sorafenib (standard care for BCLC C patients). We assumed that the BCLC B patients had a mean of three TACE treatments, whereas the BCLC C patients were given systemic therapy with sorafenib. As reported in recent studies,[11,12,24,25] we set the median survival of treated patients at 20 months for BCLC B patients, and 10 months for BCLC C patients (Table 1). As mentioned above, we assumed that Strategy A patients developing a BCLC C tumor after dropout did not receive further sorafenib therapy. We set the median survival of untreated BCLC C patients at 7 months, whereas that of untreated BCLC D patients at 4 months.[11,12,24,25] In the sensitivity analysis simulating the introduction of locoregional treatments in Strategy B patients after the first 6 months on the WL, we assumed that patients underwent one percutaneous ablation and one TACE.

Posttransplant Variables. As in recently published Markov models,[16,17] we considered an early transplant-related mortality of 5% and a long-term 5-year survival rate of 72% for patients transplanted for HCC meeting the MC.

Variables for Cost Analysis. Our analysis included all direct health-related costs (in Euros in 2008) associated with each strategy, assessed from a payer's perspective and discounted at 3% a year.[15]

The costs were obtained from the current payments within the Italian public health care system. Table 1 summarizes our hospital's mean variable costs for each procedure.

Indirect costs, such as lost earnings due to poor health, were not estimated. In Italy the cost of each sorafenib capsule is around €50. Because not all patients are able to receive the whole therapeutic dose (four capsules/day), from the proportion of patients receiving more than 80% of the planned daily dose in the Sharp trial[11] we calculated a median three capsules for each day of treatment, for each patient treated both on the WL and in BCLC stage C (after removal from the WL). For HCC patients removed from the WL due to tumor progression (patients with

BCLC stages B and C), we also considered a minimum follow-up cost for palliative care.

Calculation of the WTP for Sorafenib in Italy. Sorafenib therapy and its related costs have been accepted in Italy on the strength of the results of the Sharp trial.[11] In a Markov model specifically designed to calculate WTP, we therefore included the results of the Sharp trial and the cost per capsule accepted by the Italian public health system (Table 1).

Considering a median 5 months of time on the treatment,[11] and a median number of three capsules/day,[11] we calculated a median overall cost of the sorafenib therapy per patient at €22,500.

From the median survival times for the sorafenib and placebo groups in the Sharp trial (10.7 and 7.9 months, respectively), and using the pre-LT quality of life utility for HCC patients,[21] we calculated a crude utility of sorafenib therapy of 65 QALDs, so the calculated WTP was €346 per extra day of life.

Follow-up and Quality of Life Utilities. Patients were followed up for 10 years in the model, including periods before and after transplantation. The length of the Markov cycle was 1 day, and survival was adjusted for quality of life, based on specific utilities. Annual and monthly probabilities were converted into daily probabilities using a linear decay function.[15] Quality of life was determined for pre- and posttransplant patients by means of a systematic review of the literature, as described elsewhere.[16,17] We assumed the same utility for all HCC patients before LT whatever their tumor stage. Quality-adjusted life expectancy was discounted at a rate of 3% a year. All analyses were performed using the TreAge Prov2009 (TreAge Software, Williamstown, MA).

Sensitivity Analysis. A Monte Carlo probabilistic sensitivity analysis was used to understand the impact of variable uncertainties on the model results and to estimate the confidence that can be placed in analyzing such results. We assumed that the distribution of each variable included in our model followed a beta distribution. Moreover, we set the number of distribution samples of the Monte Carlo simulation at 1,000.

For descriptive purposes, we performed conventional one- and two-way sensitivity analyses to show the correlation between the study endpoints and specific crucial variables (sorafenib HR and median time to LT).

As mentioned above, moreover, we performed a specific sensitivity analysis simulating the introduction of locoregional therapies after the first 6 months on the WL for Strategy B patients. In particular, the model assumed that the application of conventional bridging therapies prompted a constant decrease in the dropout risk for HCC patients. In the sensitivity analysis we calculated the

value of this HR (due to locoregional therapies) that was needed to balance the benefit of sorafenib neoadjuvant therapy.

Results

Survival Benefit and Transplant Probability. To take into account the impact of variable uncertainties on the model results we performed a Monte Carlo probabilistic sensitivity analysis. According to this analysis, the median utility of Strategy A was 1,350 QALDs (10% percentile = 1,151, 90% percentile 1,434), whereas the median utility of Strategy B was 1,244 QALDs (10% percentile = 978, 90% percentile = 1,368). In Fig. 2 the distribution of incremental QALD gains of Strategy A versus Strategy B are represented: Strategy A showed a median survival benefit versus Strategy B of 94 QALDs (10% percentile = 38, 90% percentile = 210).

In the base-case analysis (Table 1), the strategy involving sorafenib treatment for HCC patients with a T2 tumor and compensated cirrhosis increased the probability of having a transplant by 5% with respect to no treatment (from 47% to 52%) if a time horizon of 10 years was considered. As a consequence, the same strategy reduced the individual risk of death by 5%, from 53% (for Strategy B) to 48% (for Strategy A). This lower mortality risk coincided with a gain of 89 QALDs for each patient treated.

In our utility-gain model, we performed one-way sensitivity analysis for all variables (Table 1). The variables most affecting the gain in LT probability and survival benefit were the HR (expressing the ability of sorafenib to delay tumor progression) and the median time to LT, as shown in Fig. 3.

As Fig. 3A clearly shows, higher median times to LT corresponded to a greater gain in transplant probability of
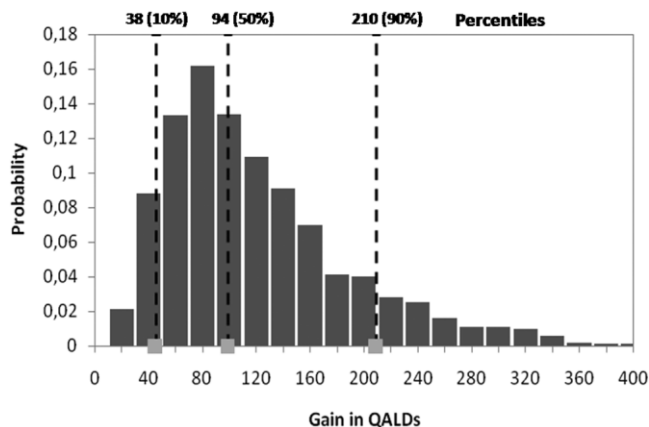

Fig. 2. Monte Carlo probabilistic sensitivity analysis: distribution of incremental gains in QALDs of Strategy A (with sorafenib before LT) versus Strategy B (without sorafenib before LT).
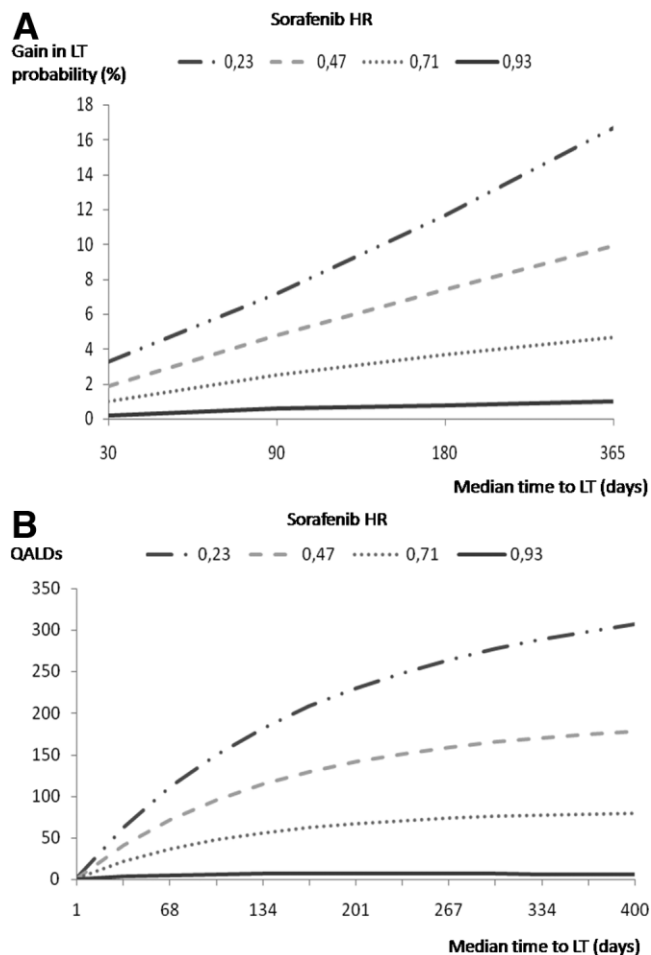

Fig. 3. Gain in LT probability (A) and in QALDs (B) of sorafenib neoadjuvant therapy as a function of sorafenib effect (HR) on time to progression of HCC (stratification subgroups) and median time to transplant (main x axis).

Strategy A versus Strategy B, and this prognostic relationship had a clearly linear behavior. The angular coefficient of this relationship, on the other hand, was strongly influenced by the particular sorafenib HR. The median time to LT and sorafenib HR also had a considerable influence on survival benefit (Fig. 3B), but this effect was almost logarithmic rather than linear.

In Fig. 4 we evaluated the impact of the sorafenib HR on the transplant prioritization (expressed as the transplant probability ratio) of HCC patients on the WL. We found an almost linear relationship between the sorafenib HR on time to tumor progression and the ratio applied to transplant probability. According to this relationship, therefore, our model found that the effect of sorafenib on tumor progression can be used to proportionally reduce the priority of HCC patients without impairing their intention-to-treat survival rate.

Cost-Utility and Cost-Benefit Analyses. In the base-case analysis, the marginal cost-utility ratio of Strategy A
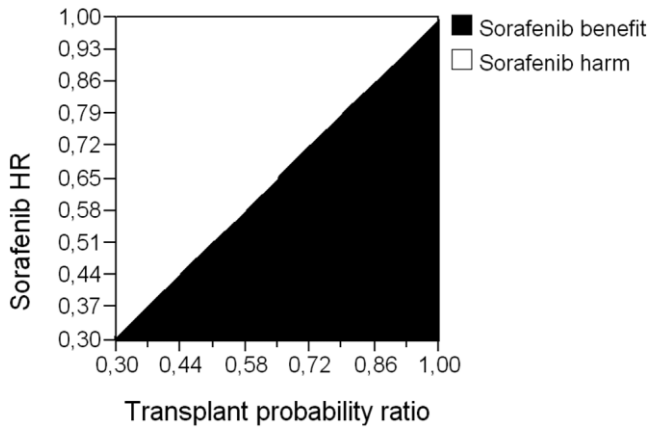
Fig. 4. Sensitivity analysis demonstrating the potential impact of the antitumoral effect of sorafenib (sorafenib HR) on patient transplant prioritization (transplant probability ratio). The transplant probability ratio threshold is the intersection between the black and white areas and equals the ratio at which the benefit of sorafenib on tumor progression is outweighed by the harm caused by a corresponding decrease in the patient's priority for transplantation.

Fig. 6. Incremental NHB between the two strategies according to sorafenib HR (A) and median time to transplant (B).

versus Strategy B was €197 per QALD, whereas the incremental NHB (assuming WTP = €346 per QALD) was 37 QALDs. Figure 5 shows that the marginal cost-utility ratios of Strategy A / Strategy B correlated strongly with the median times to LT and the sorafenib HR, but these ratios were below the calculated WTP value in the majority of cases. In particular, we found an inverse relationship between these two variables, i.e., the longer the median time to LT, the lower the HR threshold had to be in order to balance the utility against the costs.

One-way sensitivity analyses (Fig. 6) confirmed that, using the calculated WTP value, the incremental NHB of Strategy A versus Strategy B increased as the sorafenib HR decreased (Fig. 6A) and the threshold value of HR where Strategy A became harmful was 0.75.
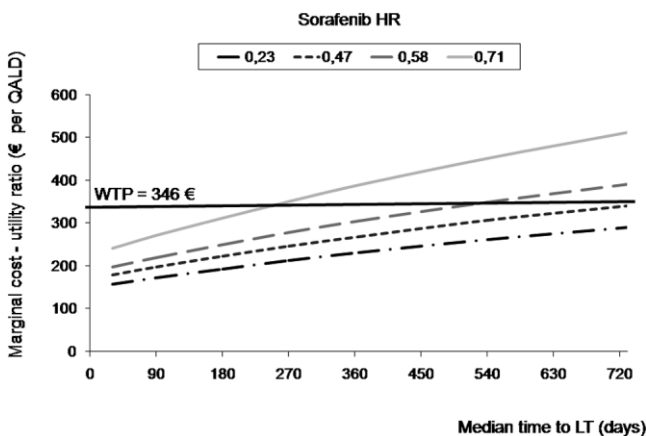

Fig. 5. Marginal cost-utility ratios afforded by Strategy A versus Strategy B as a function of median time to LT and sorafenib HR.
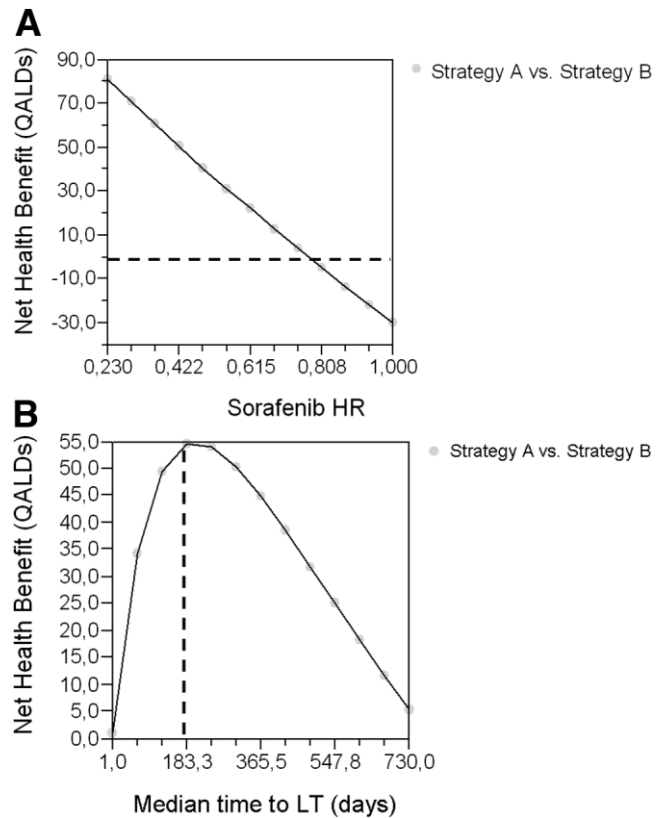
The incremental NHB tended to rise for median times to LT below 6 months (Fig. 6B), whereas it dropped for longer waiting times and only became negative more than 24 months after starting the neoadjuvant therapy.

As expected, the incremental NHB of sorafenib dropped more rapidly when locoregional therapies were introduced after the first 6 months on the WL (Fig. 7). For example, sorafenib maintained a positive NHB up to 12 months on the WL only when the impact (HR) of conventional therapies on the dropout rate was higher than 0.5 (Fig. 7).

Discussion

To the best of our knowledge, this is the first study to analyze the neoadjuvant role of sorafenib in the context of LT for HCC patients. Monte Carlo probabilistic sensitivity analysis showed with a high level of confidence (Fig. 2) that neoadjuvant therapy with sorafenib before LT had a beneficial effect on survival with respect to a strategy without therapy. This central result of our study may be essentially explained by the positive impact of sorafenib on the transplant probability of HCC patients listed for LT (Fig. 2A). Our data confirmed previous findings concerning other Markov models of pre-LT bridging therapies.[18]
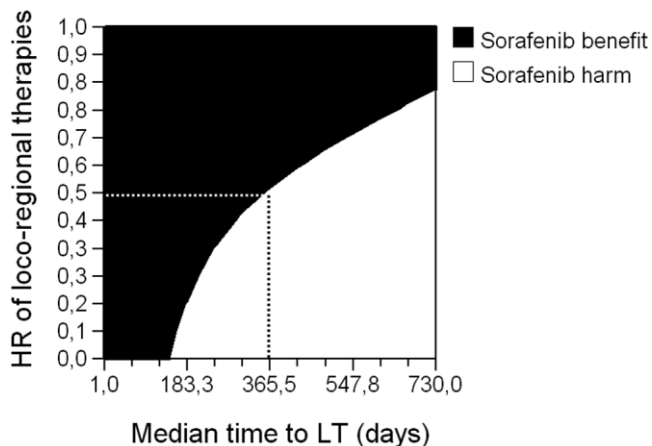
Fig. 7. Sensitivity analysis demonstrating the potential impact of introducing locoregional therapies after the first 6 months on the WL for Strategy B patients. The threshold of the locoregional therapies HR is the intersection between the black and white areas and equals the HR at which the benefit of sorafenib on Strategy A patients is outweighed by the benefit of locoregional therapies on Strategy B patients.

The results of the present study are very strong, however, because they are the first to be based on the findings of two RCTs.[12,13] In fact, whereas locoregional therapies such as TACE, percutaneous ablation, or resection[7-9] have been recommended to reduce the dropout risk for HCC candidates awaiting LT, the scientific evidence to support and quantify their efficacy against tumor progression remains weak,[11] especially as concerns the first 6 months on the WL.[10,18] For the same reason, however, it is extremely important to emphasize that the results of this study cannot be used to promote sorafenib as a first-line neoadjuvant strategy for HCC patients awaiting LT. In fact, locoregional therapies have a well-known relevant impact on the survival of early HCC patients, so they are probably more powerful bridging strategies (when properly indicated). The basic assumption of this study is that we know the effect of sorafenib (HR) on time to progression, but the same cannot be said of conventional bridging therapies. On these grounds it is structurally impossible to use this model to draw any direct comparisons between sorafenib and locoregional therapies (resection, percutaneous ablation, or TACE) as bridging strategies. On the other hand, the relationship between sorafenib and standard locoregional therapies that emerges from this study may have two facets:

1. While awaiting more robust data on the efficacy of locoregional therapies in delaying tumor progression, our model may be used to assess the utility of sorafenib as a neoadjuvant therapy before LT, and also as a more general tool for studying the role of bridging therapies, taking sorafenib as a "paradigm" due to its well-known, evidence-based beneficial effect on tumor progression.[12,13]

2. The "no bridging therapy" strategy before LT is now accepted by many centers around the world that assign HCC patients high priority for LT.[6] In this light, the results of this study can easily be transposed to clinical situations where HCC patients have low median waiting times before they receive a transplant. In real life, however, when HCC patients have prospects of longer waiting times (generally longer than 6 months) they are given locoregional bridging therapies almost everywhere. That is why our model also included a specific sensitivity analysis considering the potential introduction of locoregional therapies in Strategy B patients when their median time on the WL exceeded 6 months (Fig. 7). We took the HCC patient with a T2 tumor for reference in this study because, among the candidates meeting the Milan criteria, these characteristics identify a higher dropout risk.[17] On these grounds, many centers around the world attribute to T2 HCC patients 22 arbitrary points on the MELD score to contain the risk of tumor progression by reducing their waiting times. An excessive prioritization carries the risk of underestimating the biological aggressiveness of liver tumors,[10] however, or of harming the competing NM transplant candidates at high risk of early WL mortality (MELD score >20). Similarly, the higher transplant probability due to sorafenib (Fig. 3A) risks being beneficial for treated HCC patients but harmful for patients denied the chance of a transplant. From a population utility perspective, therefore, the individual gain in life expectancy thanks to sorafenib neoadjuvant therapy could seem irrelevant. Nonetheless, the availability of predictive models[21] that exactly correlate treatment efficacy with gain in transplant probability and survival benefit represents a potentially relevant tool for adapting the transplant priority of individual patients to a given local WL (relative proportions of HCC patients with T2 tumors and NM patients with high MELD scores).

We found a linear correlation between sorafenib HR and the transplant priority of HCC patients (Fig. 4); in this context, a second potential benefit of sorafenib neoadjuvant therapy might be its use as a corrective factor of HCC patient transplant priority in favor of NM patients with high MELD scores (Fig. 4). A minimum WL period maintaining a low risk of tumor progression (using sorafenib as bridging therapy), therefore, could be beneficial both for HCC and NM transplant candidates.

This favorable scenario changes dramatically when we consider the results of the cost-utility analysis, however. In fact, marginal cost-utility ratios increased in our model for longer times to LT or higher HR values (Fig. 4), which means that the costs of sorafenib therapy increased more rapidly than its utility according to these variables. Our study confirmed that traditional cost-effectiveness analy-

ses cannot answer the underlying moral and policy issues raised by expensive treatments, such as molecular targeted therapies.[26,27] To evaluate the threshold cost-utility of our strategy, therefore, we referred to the accepted cost-utility of sorafenib therapy in Italy, based on the results of the Sharp trial. This seemed reasonable in terms of an ethical concept of equity between patients with the same cancer, and given that the proportion of early-stage HCC candidates for LT is far lower than that of patients with intermediate or advanced tumors.

The WTP obtained was used to calculate the incremental NHB of Strategy A versus Strategy B. When this cost-utility reference was introduced, the sorafenib neoadjuvant strategy became cost-effective in almost all clinical scenarios tested in our Markov model (Figs. 4, 5). Moreover, the incremental NHB was mainly concentrated in the first 6 months on the WL, i.e., the period during which bridging therapies are currently not recommended.[10,18] Our findings, thus, suggest that different or combined bridging therapies might be adopted, depending on the median time to LT in a given area. In fact, the incremental NHB of Strategy A dropped faster when locoregional therapies were included in Strategy B (Fig. 7) according to current guidelines.[10] In such a clinical scenario, our specific sensitivity analysis supports the use of sorafenib mainly for HCC patients with median waiting times up to 12 months (Fig. 7).

There are some issues that might make our results under- or overestimate the actual benefit of sorafenib before LT. The actual benefit may be underestimated for two main reasons: (1) because a declining trend in the sorafenib HR on time to progression has been demonstrated from advanced to intermediate stage disease,[23] the actual HR range of sorafenib for T2 tumors may plausibly be lower than was assumed in our model; and (2) sorafenib acts on the molecular pathways promoting tumor dedifferentiation and microscopic vascular invasion,[25] but in this study we did not consider the potential benefit of sorafenib due to its effect on the tumor's biological aggressiveness before LT and thus on the post-LT risk of tumor recurrence.

The actual benefit of sorafenib before LT might be overestimated, on the other hand, because the antiangiogenic effect of sorafenib might have a negative effect on the outcome of surgery, although such a negative effect has never been demonstrated in the literature. This potentially toxic effect may also be more relevant in transplant candidates due to the unscheduled nature of LT (making it impossible to prudently suspend sorafenib some days before surgery) and to the presence of arterial, venous, and biliary anastomoses at risk of leakage or thrombosis. Only specifically designed clinical trials will

provide definitive data on these issues. While awaiting such data, all the findings of this study must be considered with great caution and cannot be transferred to daily clinical practice.

In conclusion, sorafenib neoadjuvant therapy is cost-effective by comparison with no therapy for T2-HCC patients waiting for LT, particularly for median times to LT under 6 months. This Markov decision analysis, therefore, strongly supports the need for designing clinical trials in this complex field to comprehensively study the safety profile of sorafenib used before LT.

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