

Original article

Patients' preferences for adjuvant sorafenib after resection of renal cell carcinoma in the SORCE trial: what makes it worthwhile?

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ABSTRACT

Background

We sought to determine the survival benefits that patients judged sufficient to warrant adjuvant therapy with sorafenib for 1 year, or for 3 years after resection of renal cell carcinoma (RCC) in the SORCE trial.

Methods

SORCE participants from all sites in Australia and New Zealand, and selected sites in the UK, completed a validated preferences questionnaire at months 0, 3, 15 and 42 to elicit the minimum survival benefits they judged sufficient to warrant adjuvant sorafenib for 1 year (versus observation), or for 3 years (versus 1 year). The questionnaires used reference survival times of 5 years and 15 years; and reference survival rates at 5 years of 65% and 85%.

Findings

The 233 participants had a median age of 57 years (range 29 to 78) and 71% were male. For 1 year of sorafenib versus no adjuvant therapy, the median benefits in survival times judged sufficient to warrant treatment were an extra 9 months beyond 5 years and an extra 1 year beyond 15 years; the median benefit in survival rates were an extra 4% beyond 65% and an extra 3% beyond 85% at 5 years. For 3 years of sorafenib versus 1 year of sorafenib, the median benefit in survival time judged sufficient to warrant extended treatment was an extra 1 year beyond both 5 years and 15 years. Participants randomly allocated treatment with sorafenib judged larger benefits necessary than those allocated placebo. Participants' preferences were not associated with their baseline characteristics or the interval from randomisation.

Conclusion

Most participants judged an extra year of survival necessary to warrant 1 year of adjuvant sorafenib worthwhile, and an additional year of survival to warrant extending the duration of sorafenib from 1 year to 3 years. Patients' preferences are important in shared-decision-making.

SORCE trial clinical trials number = NCT00492258

KEYWORDS

Renal cell carcinoma

Sorafenib

Adjuvant therapy

Patients' preferences

Decision-making

KEY MESSAGE

Preferences studies determine how patients trade-off the benefits and harms of a cancer treatment. Patients in the SORCE trial of adjuvant sorafenib in renal cell cancer judged an extra 1 year of survival time and an extra 3-4% survival rate necessary to justify taking one year of adjuvant sorafenib. An extra 1 year was needed to justify taking three years of adjuvant sorafenib.

INTRODUCTION

Surgery is the mainstay of curative treatment for RCC, but high rates of recurrence (up to 40%) highlight the need for effective adjuvant therapy. [1] Recent trials of adjuvant oral tyrosine kinase inhibitors were initiated due to their efficacy in metastatic RCC. [2, 3] SORCE (NCT00492258) is one such trial as a double-blind, placebo-controlled, randomised phase 3 trial comparing adjuvant sorafenib for 1 year (n=642) or 3 years (n=639) versus observation alone (N=430) after resection of localised RCC at intermediate or high risk of recurrence that recruited from 147 sites worldwide. The SORCE trial accrued 1711 patients globally and the main efficacy results are awaited.

Sorafenib is a VEGF tyrosine kinase inhibitor given orally twice daily with proven efficacy in advanced RCC, hepatocellular carcinoma and thyroid cancer. [3-5] Side effects of sorafenib are common and typical of VEGF inhibitors. In advanced RCC, [3] the most common all grade side effects of sorafenib versus placebo were diarrhoea (43% v 13%), rash (40% v 16%), fatigue (37% v 28%), hand-foot skin reactions (30% v 7%), and alopecia (27% v 3%) with significantly more severe (grade 3 or 4) hypertension (4% v <1%, p=0.001) and hand-foot skin reaction (6% v 0%, p<0.001).

Preference studies reveal how individuals trade-off the potential benefits, harms and inconveniences of a treatment by determining the minimum benefits they judge sufficient to make the treatment worthwhile. They are especially relevant to adjuvant therapies where individuals must weigh up modest survival benefits only realised in time by no recurrence of their cancer with side effects predominantly experienced whilst on the treatment. We previously reported, for example, that over 50% of women who had adjuvant chemotherapy for early breast cancer judged a 1% improvement in 5 year survival rates sufficient to make it worthwhile.[6] Larger survival benefits were required for longer duration adjuvant hormonal

therapy where over 50% of women required at least 5% improvement in 5 year survival rates to make it worthwhile.[7]

Adjuvant therapy with sorafenib for 1 to 3 years as in the SORCE trial presents a distinct range of side effects and inconveniences. There are no published studies of the benefits judged necessary to make sorafenib or other oral VEGF inhibitors for RCC worthwhile in the adjuvant setting. Therefore, the aim of this study was to determine the minimum benefits judged sufficient to make adjuvant sorafenib worthwhile in resected RCC, and the factors influencing these preferences, by surveying a subgroup of participants in the SORCE trial.

METHODS

We conducted a cohort study nested within the SORCE trial at all 22 sites in Australia and New Zealand (ANZ) and 30 of 87 sites in the United Kingdom (UK). The preferences study was offered to all SORCE participants in ANZ, but was optional for participants in the UK. The only additional eligibility criterion was sufficient English literacy to complete the questionnaires. Ethics approval was obtained for all sites and all participants provided signed, written, informed consent.

Preferences questionnaire

Preferences were elicited with a self-completed, validated questionnaire administered at baseline before randomisation, and then at 3, 15 and 42 months after randomisation ('post-baseline').[8] The questionnaire used hypothetical scenarios to determine the smallest survival benefits judged sufficient to warrant 1 year of adjuvant sorafenib versus no adjuvant sorafenib, and 3 years of adjuvant sorafenib versus 1 year of adjuvant sorafenib.

Two types of scenario were used to evaluate 1 year of sorafenib versus no sorafenib. The first involved survival times, and the second involved survival rates. Survival time scenarios asked participants to choose between a reference survival time *without* the side effects and inconvenience of sorafenib (e.g. 5 years) versus a series of longer survival times *with* the side effects and inconvenience of sorafenib for 1 year, ranging from an extra 1 month to an extra 15 years. Survival rate scenarios asked participants to choose between a reference survival rate at 5 years *without* the side effects and inconvenience of sorafenib (e.g. 65%) or a series of survival rates at 5 years *with* the side effects and inconvenience of sorafenib for 1 year. The survival rates with sorafenib ranged from an extra 1% to a maximum survival rate of 100%. The endpoint for each scenario was the minimum benefit for which the participant chose sorafenib rather than placebo. Additional survival time

scenarios were used to evaluate the benefits needed to warrant extending the duration of sorafenib from 1 year to 3 years.

The reference survival times (5 years and 15 years) and survival rates (65% and 85% at 5 years) were based on data from previous trials and chosen to reflect the range of typical prognoses for patients with intermediate and high risk RCCs. [9, 10]

Other assessments

Participants' baseline characteristics were collected with a study-specific questionnaire. Details of their disease and surgery were extracted from the case report forms for SORCE. Participants' expectations at baseline (i.e. before they had started their allocated trial treatment) of their health-related quality of life (HRQL) during adjuvant therapy with sorafenib were assessed with the Patient Disease and Treatment Assessment Form (Patient DATA Form). [11]

Statistical analysis

Bar charts combining all three randomly allocated treatment groups are used to show the cumulative distributions of the minimum benefit judged sufficient at baseline (before starting blinded adjuvant therapy). Predictors of the survival gains (i.e. average response to the two survival time questions) judged sufficient at baseline to justify 1 year of sorafenib were explored with multivariable linear regression following normal score transformation of the highly skewed values, [12] as in our previous studies. We used the median as the measure of central location to summarise the preferences of groups, i.e. the smallest benefit judged sufficient by at least 50% of that group.

Comparisons between randomised treatment groups on the preference questions at 3, 15 and 42 months were performed using mixed models for repeated measures (MMRM) after

normal score transformation. The minimum benefits judged sufficient at baseline (before starting treatment), the post-baseline time point (3, 15, and 42 months after starting treatment), and the randomly allocated treatment (sorafenib versus placebo) were fitted as fixed effects. Models including an interaction term between treatment allocation and post-baseline time point were used to determine if the treatment effect varied over time. Models without this interaction term imply a treatment effect that is constant over time.

The planned sample size of 300 participants was based on the expected recruitment of 200 from ANZ, and an additional 100 from the UK. The total accrual of 233 was somewhat lower than expected, and yields 95% confidence intervals no wider than ± 7 percentage points for percentages based on all participants.

RESULTS

Baseline characteristics of the participants are summarised in Table 1. The mean age was 57 years (range 29 to 78). Most participants were male (71%), and had cancers that were <10cm in size (69%) with clear cell histology (86%). Participants' ratings at baseline of their expectations about HRQL during adjuvant therapy with sorafenib are summarised in Supplementary Table 1. The three symptoms expected to be most troublesome were fatigue, skin rash, and sore hands or feet; the three aspects of well-being expected to be worst affected were energy, mood, and appetite.

Participants' preferences for adjuvant sorafenib at baseline are shown in Supplementary Figures 1, 2 and 3. For 1 year of sorafenib versus no adjuvant therapy, the median benefits in survival time judged sufficient (by at least 50% of participants) were an extra 9 months beyond 5 years and an extra 1 year beyond 15 years; the median benefit in survival rate judged sufficient was an extra 4% beyond 65% and an extra 3% beyond 85% at 5 years. For 3 years of sorafenib versus 1 year of sorafenib, the median benefit in survival time judged sufficient was an extra 1 year beyond both 5 years and 15 years.

Preferences were skewed to the right, meaning that over 50% of participants judged benefits smaller than the mean were sufficient to make adjuvant sorafenib worthwhile, and there was a tail in the distribution of participants judging benefits larger than the median necessary to make adjuvant sorafenib worthwhile. Neither baseline characteristics nor pre-treatment expectations of HRQL during adjuvant therapy were significantly associated with preferences.

Table 2 shows the effects of the randomly allocated treatment (sorafenib versus placebo), and time point (experienced treatment duration 0, 3, 15 or 42 months) on participants' preferences for 1 year of sorafenib versus no adjuvant therapy. At baseline

(before starting treatment) the median benefits judged sufficient were moderate in both randomly allocated treatment groups (6-12 months, 2-5%). Participants randomly allocated sorafenib judged numerically larger benefits necessary at baseline than those allocated placebo, simply due to the play of chance. The MMRM analysis accounting for this chance imbalance at baseline, and allowing for a variable treatment effect over time, indicated statistically significant differences in preferences at 3 months for the two survival time scenarios ($p=0.036$ for 5 year reference and $p=0.032$ for 15 year reference), and at 15 months for the survival rate scenario with reference survival rate of 65% at 5 years ($p=0.015$). There was, however, no compelling statistical evidence that the treatment effect varied over post-baseline time points (interaction p -value was non-significant). The MMRM analysis without this interaction term (implying the treatment effect was constant over post-baseline time points) yielded similar results and conclusions with statistically significant differences for the two survival time scenarios ($p=0.043$ for 5 years and $p=0.016$ for 15 years), and the survival rate scenario with a reference 5-year survival rate of 65% ($p=0.023$).

The effects of the randomly allocated treatment and time point on preferences for 3 years of sorafenib versus 1 year of sorafenib are shown in Table 3. Post-baseline, there was again a tendency for participants allocated sorafenib, rather than placebo, to judge larger benefits necessary to warrant the extra 2 years of adjuvant sorafenib. The MMRM analysis accounting for any baseline differences, and allowing the magnitude of the treatment effect to vary over time, yielded no statistically significant differences according to randomly allocated treatment group. There was furthermore no compelling statistical evidence that the treatment effect varied over time. The MMRM analysis without this interaction term yielded a statistically significant difference for the survival time scenario with a reference survival time of 5 years ($p=0.038$), but not 15 years.

DISCUSSION

Most participants judged moderate survival benefits necessary (sufficient) to make adjuvant sorafenib worthwhile in the SORCE trial. Preferences were, however, highly variable between individuals. Preferences were influenced by the planned duration of adjuvant therapy: approximately double the benefit was required to warrant sorafenib continued for 3 years rather than for 1 year. Participants who were randomly allocated sorafenib, and therefore experienced its side effects, generally required larger benefits than those who were randomly allocated placebo.

Comparisons of patients' preferences for adjuvant sorafenib in this trial with patients' preferences for other adjuvant therapies elicited using similar methods provide context for these results. The median benefits judged sufficient by participants for sorafenib in this study (an extra 9-12 & an extra 3-4%) were considerably larger than those required to make worthwhile adjuvant chemotherapy for either breast cancer or colon cancer (an extra 1 day to 1 month & an extra 0.1% to 2%).[6, 8]. Preferences for adjuvant sorafenib in this study were more similar to preferences for adjuvant chemotherapy in non-small-cell lung cancer (median benefits of an extra 9 months to 1 year), [13] intraperitoneal chemotherapy for advanced ovarian cancer (median benefits of an extra 6 months and 5%), [14] and adjuvant chemotherapy for endometrial cancer in the PORTEC-3 trial (median benefits of an extra 1 year and 5%).[15]

The results of three large, randomized, phase 3 trials of adjuvant therapy with oral VEGF-targeted tyrosine kinase inhibitors have recently been reported: S-TRAC comparing 1 year of sunitinib ($n=309$) versus placebo ($n=306$), [16] ASSURE comparing 1 year of sunitinib ($n=647$) and sorafenib ($n=649$) versus placebo ($n=647$), [17] and PROTECT comparing 1 year of pazopanib ($n=571$ in ITT 600mg group) versus placebo ($n=564$ in ITT

600mg group).[18] Only S-TRAC was positive for its primary end point with an absolute improvement in disease free survival (DFS) at 3 years of 5.4% (from 59.5% to 64.9%, HR 0.76). All three trials showed no overall survival (OS) benefit, but this data was immature. The SORCE trial was designed to detect an absolute improvement in DFS at 3 years of 7.5% (from 63.5% to 71%) reflecting a target hazard ratio (HR) of 0.75, similar to that reported in the S-TRAC trial.

The toxicity of adjuvant sorafenib in the SORCE trial has not yet been reported, but it is the likely cause of differences in preferences between the treatment groups after randomisation. Toxicity results from the S-TRAC, ASSURE, and PROTECT trials showed that clinically important adverse events and treatment discontinuations were frequent. Both ASSURE and PROTECT had high rates of discontinuation early in the trials (45% for sorafenib and 44% for sunitinib in ASSURE; 39% for pazopanib in PROTECT) leading to protocol amendments for lower starting doses and consequent lower rates of discontinuation (30% for sorafenib and 34% for sunitinib in ASSURE; 35% for PROTECT).[17, 18]

The different outcomes of 1 year of adjuvant targeted therapy observed in S-TRAC, ASSURE and PROTECT have increased interest in the outcomes of 3 years of adjuvant sorafenib in the SORCE trial. Our findings indicate that a typical participant who had experienced adjuvant sorafenib judged that to warrant continuing it for 3 years, a median survival gain of an additional 9-12 months would be required, above and beyond the 9-12 months required to make the initial 1 year of adjuvant therapy worthwhile. These findings highlight the trade-offs inherent in extending the durations of adjuvant therapy, and correspond with our studies in early breast cancer which also demonstrated that much larger benefits were needed to warrant 5 years of adjuvant endocrine therapy (e.g. an extra 3-5 years) than to warrant 3-6 months of adjuvant chemotherapy (e.g. an extra month).[6, 7]

The major strength of our study is its nested, longitudinal design within a large-scale, placebo-controlled, randomised trial. This allowed unbiased comparisons of preferences before and after experiencing both adjuvant sorafenib and placebo. Participants who experienced sorafenib required larger benefits to make it worthwhile than those who experienced placebo, as expected. However, participants allocated placebo continued to judge small to moderate benefits necessary to warrant adjuvant therapy, even after experiencing a treatment with no adverse effects for 3, 15 and 42 months, suggesting that the inconvenience of daily therapy, and the idea of taking it, are significant considerations.

The main limitations of this study stem from our use of hypothetical scenarios in trial participants. Our results and conclusions apply directly to people willing and able to participate in a randomised trial, and to complete moderately complex questionnaires, but they may not be as applicable to other people. We used the same hypothetical scenarios to elicit preferences in all participants. Each individual's preferences reflected their own knowledge and experience of study treatment (sorafenib or placebo). However, their preferences were based on hypothetical baseline survival rates and times without adjuvant therapy, rather than an individualised estimate based on their own personal characteristics and those of their tumour.

The clinical implications of our study are that people with recently resected RCC facing decisions about adjuvant therapy with a VEGF targeted agent deserve detailed information and careful consideration about its possible benefits, harms, and inconveniences, particularly its duration. Patients' preferences are highly variable, and unpredictable, so they must be elicited individually rather than guessed according to their demographics or tumour characteristics. Discussions and decisions about adjuvant therapy should be personalised to account for each individual's values, attitudes, circumstances, and preferences. This will become even more important as new agents with different toxicity profiles and extended

durations, such as the immune checkpoint inhibitors, undergo testing as adjuvant systemic therapy in RCC and other cancers.

Our study supports the feasibility, validity, and usefulness of incorporating preference studies in large scale randomised trials. Preference studies can provide useful and unique information about how participants value, weigh, and trade-off the possible benefits, harms, and inconveniences of study treatment. Data from preferences studies complement the information routinely collected and reported in clinical trials, and should help future patients and clinicians facing decisions about adjuvant therapy.

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CONFLICTS OF INTEREST

ID Davis is a member/ chair of following industry advisory boards: Pfizer Renal Cell Carcinoma, Novartis, BMS ipilimumab, BMS anti-PD1, Bayer Nexavar, Roche Genitourinary Cancers, AstraZeneca Immunotherapy, and Eisai. No personal remuneration is received for any of this work. All payments or honoraria are paid directly to ANZUP Cancer Trials Group. ID Davis is the director and chair of the Board of ANZUP Cancer Trials Group. No personal remuneration is received for any of this work. ANZUP led the SORCE trial in Australia with funding support from Bayer Australia. ANZUP has received funds from Novartis to perform the EVERSUN trial. ANZUP has funding agreements to support clinical trials in renal cell carcinoma from MSD, Amgen and BMS.

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All other authors declared no conflict of interest.

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SUPPLEMENTARY FIGURE LEGENDS

Figure 1. Cumulative proportions of patients considering whether 1 year of sorafenib (versus no adjuvant therapy) is worthwhile for various improvements in 5 year & 15 year reference survival times

Figure 2. Cumulative proportions of patients considering whether 1 year of sorafenib (versus no adjuvant therapy) is worthwhile for various improvements in 65% & 85% reference survival rates

Figure 3. Cumulative proportions of patients considering whether 3 years of sorafenib (versus 1 year of sorafenib) is worthwhile for various improvements in 5 year & 15 year reference survival times