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Overall Survival Endpoint in Oncology Clinical Trials: Addressing the Effect of Crossover. The Case of Pazopanib in Advanced Renal Cell Carcinoma

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Running title: Pazopanib Crossover in Advanced RCC

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ABSTRACT

Objective: To identify the issues of using overall survival (OS) as a primary endpoint in the presence of crossover and the statistical analyses available to adjust for confounded OS due to crossover in oncology clinical trials. ***Methods:*** An indirect comparison was conducted between pazopanib and sunitinib in advanced renal cell carcinoma. Statistical adjustment methods were used to estimate the true comparative effectiveness of these treatments. Recently, a head-to-head trial comparing pazopanib and sunitinib was completed. This provided the opportunity to compare the OS treatment effect estimated for pazopanib versus sunitinib using the indirect comparison and statistical adjustment techniques to that observed in the head-to-head trial. ***Results:*** Using a rank-preserving structural failure time model to adjust for crossover in the pazopanib registration trial, the indirect comparison of pazopanib versus sunitinib resulted in an OS hazard ratio (HR) of 0.97, while an unadjusted analysis resulted in an OS HR of 1.96. The head-to-head trial reported a final OS HR of 0.92 for pazopanib versus sunitinib. ***Conclusion:*** This case study supports the need to adjust for confounded OS due to crossover, which enables trials to meet ethical standards and provides decision makers with a more accurate estimate of treatment benefit.

Key Words

Crossover, Overall survival, Pazopanib, Renal cell carcinoma

INTRODUCTION

Over the last decade, there has been debate over licensing and reimbursement of new oncology agents [1]. Although various stakeholders (e.g., clinicians, regulators, payers) may be interested in a number of different clinical trial endpoints, overall survival (OS) is seen as the gold standard, and demonstrating improved OS is the desired outcome of any therapy [2,3]. Overall survival (time from study randomization to time of death due to any cause) is usually measured using the intent-to-treat (ITT) analysis [4], in which participants are analyzed in their assigned treatment group regardless of actual treatment received [5]. Overall survival is an advantageous clinical trial endpoint because it is simple to measure, is unambiguous, and is not subject to investigator or assessment bias [6]. However, use of OS as a primary endpoint is problematic if treatment crossover confounds the results.

Crossover is defined as patients in the control group receiving experimental treatment after a primary endpoint has been reached (e.g., disease progression). Here we present a case study in advanced renal cell carcinoma (aRCC) that highlights the issues of using OS as a primary endpoint in the presence of crossover and the statistical analyses that are available to adjust for confounded OS due to crossover.

BACKGROUND

Treatment crossover and receipt of post-study therapies

Oncology trials frequently use progression-free survival (PFS) as the primary endpoint, and regulatory submissions are frequently based on achieving a statistically significant improvement in this endpoint [7]. Improved PFS might lead to an ethical imperative to allow patients in the control arm to receive the experimental treatment upon disease progression [8-10]. The potential for crossover after a favorable PFS analysis also makes enrollment in a clinical trial more attractive to patients as it will allow them access to the investigational treatment regardless of the initial intervention [11,12]. Treatment crossover can cause the OS treatment effect associated with the experimental therapy compared with control to be underestimated if an ITT analysis is used because a number of patients in the control arm will have received the experimental treatment and may have consequently experienced a clinical benefit [10].

Furthermore, the growing number of oncology therapies has increased the availability of second- and third-line treatments that can improve survival. Patients enrolled in a clinical trial may receive a variety of post-study anticancer treatments following disease progression. If post-study therapies differ across treatment arms and have effects on OS, then comparisons of OS between randomized treatments may be similarly confounded as with treatment crossover. To the extent that receipt of post-study therapies do not constitute the standard treatment pathway, it may be appropriate to adjust estimates of OS for differences between groups in the receipt of these treatments to obtain estimates of the likely difference between randomized treatments under conditions of typical clinical practice.

Because of these issues, there is a need for consensus among all interested parties on a transparent, consistent, and timely evaluation of the foregoing factors when selecting primary endpoints in oncology trials. Consensus might also be required to better define what post-study

treatments should be allowed in a clinical trial to ensure that similar and realistic treatment options are available for study participants. In the meantime, the ethical rationale supporting treatment crossover in oncology trials and its confounding effects on survival estimates pose specific fundamental challenges.

Statistical approaches to adjust for crossover

Advanced statistical approaches such as inverse probability of censoring weighted (IPCW) marginal structural models and rank-preserving structural failure time (RPSFT) models have emerged to control for the confounding effect of crossover in OS results [13,14]. These techniques have been progressively applied in the context of health technology assessments (HTA) as they seem to overcome key fundamental limitations derived from the application of more naive analyses. Simple approaches, such as censoring or excluding patients who switch treatments, or incorporating a treatment indicator as a time-dependent covariate, are prone to substantial selection bias [10,13,15]. The more sophisticated IPCW and RPSFT techniques have important advantages but are not free from potential limitations associated with the inherent assumptions upon which their structural model is based.

In simple terms, the IPCW method aims to adjust for crossover by recreating the population that would have been evaluated if crossover had not occurred. The main advantage of the IPCW analysis is that estimation of the OS benefit under the counterfactual scenario (i.e., a hypothetical situation whereby control patients had not crossed over) is based on extensive data for baseline and time-dependent covariates collected during the trial. However, this strength is also its main limitation, as IPCW assumes that all the relevant covariates that can predict the crossover of patients and that are prognostic for survival have been identified and included in the model [10,16-20]. Therefore, IPCW estimates are unbiased only to the extent that the model includes all potentially relevant predictors of crossover and survival.

The RPSFT method estimates the difference in OS between treatment groups that would have been observed if crossover had not occurred. This method proportionally shrinks the estimated amount of additional survival conferred to patients who crossed over according to the treatment effect estimate for the experimental treatment. In its estimation procedure, the RPSFT method relies upon the randomization of the trial; it assumes that, in the absence of treatment in either of the randomized groups, average survival between groups would have been equal. However, some key assumptions, which are often unverifiable, need to be fulfilled [21]. First, the effect of experimental treatment on OS is the same irrespective of when treatment is given in a patient's disease course, relative to the duration of time the treatment is received. Second, absolute OS benefit of an experimental treatment never exceeds actual treatment time. And third, all patients receive identical benefit from an experimental treatment. It is especially noteworthy that there cannot be subsets of patients particularly responsive to treatment.

It has been suggested that HTA bodies would benefit from evaluating a range of sensitivity analyses exploring various methodologies when assessing the OS benefit of new oncology interventions [13,22]. Health technology assessment bodies are making increasing use of these analyses; however, clinicians, investigators, and payers may not be as familiar with these techniques.

Case Study: Pazopanib and Sunitinib in aRCC

It should be acknowledged that a number of issues are embedded in this case study (e.g., limitations of conducting indirect comparisons, methods to control treatment crossover in the sunitinib trial). Our objective was to provide an example of a situation where treatment crossover had confounded treatment effect estimates, and to show how statistical adjustment methods were utilized to address this issue. This case study is of particular value due to the existence of the head-to-head COMPARZ study, which allows an assessment of the accuracy of the adjustment methods used.

Pazopanib versus BSC

This case study is based on the National Institute for Health and Care Excellence (NICE) Technology Appraisal [23], which focused on the phase III, randomized, controlled trial VEG105192 that compared pazopanib plus best supportive care (BSC) to BSC alone in treatment-naive patients with aRCC [24]. The technology appraisal assessed the clinical and cost-effectiveness of pazopanib in treatment-naive patients with aRCC when compared with sunitinib, interferon, and BSC.

The primary analysis of VEG105192 was based on the ITT population, which included the treatment-naive subpopulation (n = 233) and the cytokine-pretreated subpopulation (n = 202). Patients who experienced disease progression could receive further anticancer therapy at the discretion of the attending physician according to the standard of care in the region. Pazopanib was offered as a treatment option for those patients who were found to have progressed on BSC alone (after unblinding) via an open-label extension study (VEG107769) [25]. To avoid bias and maintain the integrity of the VEG105192 trial, unblinding was conducted by an independent party. Enrollment in VEG107769 was almost entirely concurrent with

enrollment in the VEG105192 parent study, allowing placebo patients the opportunity to cross over to pazopanib immediately upon disease progression.

The median time from date of randomization into the placebo arm of VEG105192 to the first dose of pazopanib (in VEG107769) was 8.1 months; the minimum time was 2 months (Table 1). Approximately twice as many patients received post-study anticancer treatments following disease progression in the placebo arm than in the pazopanib arm (64% versus 34%, respectively), largely due to crossover to pazopanib (51% of BSC patients crossed over to pazopanib) [24]. The percentage of patients receiving pazopanib was nearly equal in both arms of the VEG105192 study after approximately 1 year (fig. 1). The primary endpoint was PFS, which was significantly prolonged in the pazopanib group compared with the placebo group (median, 9.2 vs 4.2 months; hazard ratio [HR] = 0.46; 95% confidence interval [CI] 0.34–0.62; $p < 0.0001$). The Kaplan-Meier curves for final OS in the treatment-naive population are shown in fig. 2. There is a distinct separation of the curves early on; the curves subsequently cross at approximately 20 months, which likely reflects the effect of placebo patients crossing over to pazopanib. Consequently, the utility of the ITT OS analysis was limited because of the substantial level of crossover. Median OS from the start of pazopanib treatment in all treatment-naive patients randomized to the experimental group in VEG105192 (n = 155) was 22.9 months (95% CI 17.6–25.4 months) and was 22.7 months (95% CI 13.9–34.0 months) in patients who crossed over to pazopanib treatment (n = 40). The details of the trial results and the NICE assessment are presented in Supplementary Table S1.

A wide range of analyses was conducted to adjust the OS results for the crossover of BSC patients to pazopanib upon disease progression (Table 2). Taken as a whole, the results indicate that among treatment-naive patients pazopanib therapy is associated with a relevant survival benefit compared with placebo. The adjusted HRs for OS for pazopanib versus placebo ranged from 0.300 to 1.075, depending on the methodology and whether they were adjusted for baseline patient characteristics. The weighted RPSFT method was identified as the optimal

adjustment technique in this case due to the benefits of this methodology in preserving randomization and avoiding the IPCW assumptions of no unmeasured confounders. In addition, the OS HR of 0.501 derived from the RPSFT method lies within the range of estimates obtained by applying alternative methodologies [18,23]. Finally, the similar median OS results between pazopanib and BSC in the treatment-naive population suggest that the benefit of pazopanib is similar regardless of whether the patient had previously been randomized to placebo and then progressed or had started immediately on pazopanib—satisfying a key assumption of the RPSFT method. The NICE appraisal committee acknowledged that the ITT estimates of OS for pazopanib versus BSC had been confounded by treatment crossover in more than half of the BSC patients upon disease progression. The committee endorsed the use of RPSFT in the base-case analyses, but noted that the CI around the derived OS HR was very wide (0.136–2.348). The committee concluded that there was sufficient evidence that pazopanib increased survival compared with BSC despite uncertainty about the precise magnitude of the OS gain [18,23].

Indirect comparison of pazopanib versus sunitinib

As no head-to-head trials evaluating the efficacy of pazopanib versus other active therapies were available at the time of the NICE submission, an indirect comparison of pazopanib versus comparator interventions (sunitinib, interferon alfa [IFN-α], and BSC) was conducted. Along with the VEG105192 study, one study of sunitinib versus IFN-α (A6181034) [26] and pooled results from four studies of IFN-α versus control therapies [27-30] identified in a Cochrane review of immunotherapies for aRCC [31] were included in the indirect comparison. The sunitinib versus IFN-α trial demonstrated that sunitinib treatment provided an OS advantage compared with IFN-α (median 26.4 vs 21.8 months, respectively; HR = 0.821; 95% CI 0.673–1.001; p = 0.051) [26]. This study was also confounded by crossover, as patients in the IFN-α group were allowed to receive sunitinib upon disease progression. The sponsor (Pfizer)

conducted an exploratory analysis to exclude patients who received post-study anticancer treatment, which resulted in a median OS with sunitinib that was twice that of IFN-α (28.1 vs 14.1 months, respectively; HR = 0.647; 95% CI, 0.483–0.870; p = 0.003) [26]. The HR from this analysis was used in the indirect comparison of pazopanib and sunitinib (Table 3) and was part of the GSK submission to NICE for pazopanib. Results of the base-case indirect comparison for OS using the weighted RPSFT-derived HR for OS for pazopanib versus placebo showed that pazopanib had a similar survival benefit compared with sunitinib in treatment-naive patients (HR = 0.97; 95% CI 0.36–2.61).

Head-to-head comparison of pazopanib versus sunitinib (COMPARZ)

The head-to-head COMPARZ study, designed to demonstrate non-inferiority of pazopanib versus sunitinib with respect to PFS in patients with aRCC who had not received prior systemic therapy for advanced or metastatic RCC, has now reported the final OS as being similar in both groups (HR = 0.92; 95% CI 0.79–1.06) [32]. Table 3 shows the HRs for OS for pazopanib versus sunitinib in treatment-naive patients estimated from the indirect comparisons based on VEG105192 using both the ITT analysis (OS confounded by crossover) and the HR derived from the RPSFT methodology to account for crossover. The point estimate from COMPARZ is similar to that derived from the indirect comparison based on the RPSFT-adjusted HR from VEG105192, thus supporting that approach to adjusting for treatment crossover. In addition, the HRs for PFS from COMPARZ based on independent review (HR = 1.0466; 95% CI 0.8982–1.2195) and investigator assessment (HR = 0.998; 95% CI 0.863–1.154) were also comparable to the HR for PFS for pazopanib versus sunitinib from the indirect comparison conducted for the NICE technology assessment (HR = 0.972; 95% CI 0.590–1.60). Of note, while treatment crossover was not permitted in the COMPARZ trial, both treatment groups were allowed to receive post-study therapies.

DISCUSSION

Results of this case study demonstrate that estimates of the relative effectiveness of pazopanib versus sunitinib on OS produced by an indirect treatment comparison using OS data from the treatment-naive population of VEG105192 trial that were adjusted for treatment crossover using the RPSFT method are similar to OS results from the direct head-to-head comparison of pazopanib and sunitinib in COMPARZ. These findings provide indirect confirmation that the effect of pazopanib versus BSC on OS in the ITT analysis of VEG105192 was confounded by crossover, and that the RPSFT-adjusted OS from VEG105192, combined with the indirect treatment comparison of trials of IFN-α vs BSC and sunitinib vs IFN-α, yielded an accurate estimate of the relative effectiveness of pazopanib and sunitinib. Therefore, this case study demonstrates that statistical methods that adjust for treatment crossover can produce accurate and useful results, which may be different compared to those obtained from ITT analyses.

This case study focused primarily on the effects of direct treatment crossover (from the control group onto the experimental treatment group) in the VEG105192 trial. As noted above, the receipt of post-study anticancer treatment can also lead to differences in OS between randomized treatment groups. The differential receipt of post-study anticancer treatments across randomized treatment groups may pose a problem for regulators and reimbursement agencies attempting to interpret study results for OS if the post-study anticancer treatments are not representative of standard care pathways. In these instances, it may be appropriate to attempt to adjust for both direct treatment crossover and receipt of post-study anticancer treatment. However, adjustment of OS for differences between randomized treatment groups in receipt of post-study anticancer treatments poses different challenges and requires different methods than for adjustment of treatment crossover.

There is a need for a wider and more candid understanding of the challenges of measuring effects on OS in oncology trials. The ethical imperative to permit treatment crossover in trials of cancer therapies, along with the advent of more effective second- and third-line anticancer therapies, is likely to make detection of OS improvements in confirmatory phase III studies increasingly difficult. Furthermore, the need for very long follow-up periods and larger sample sizes in order to capture OS data will likely make the collection of mature OS data an unrealistic target. While discussion on the use of OS as a pivotal clinical endpoint for licensing and reimbursement may be necessary, given the current drug development and clinical trials environment, OS is highly likely to remain an important outcome measure.

When planning clinical trials that include OS as a primary or secondary endpoint, investigators should make a careful assessment of whether and when treatment crossover is necessary or appropriate. Similar deliberations should be conducted with respect to differential receipt of post-study anticancer treatment. If it is determined that crossover and/or differential receipt of post-study treatment will be allowed, investigators should take into consideration whether statistical adjustment of OS will be conducted. The methods that will be used in these analyses should be specified *a priori*, and efforts should be made to ensure that data necessary to conduct robust analyses are collected during the course of the trial.

A limitation of this case study is that a naive method was used in the indirect comparison to adjust for treatment crossover in the sunitinib trial. It would have been preferable if a more appropriate method had been used, such as RPSFT or IPCW. Despite this, the indirect comparison produced estimates of the relative effect on OS of pazopanib and sunitinib that were similar to the OS seen in the head-to-head COMPARZ trial. This would suggest that, in this case, the naive method used to adjust for crossover in the sunitinib trial did not lead to substantial bias.

An analytical framework has been developed to inform NICE, associated academic groups, and manufacturers on the best methods available to control for treatment crossover

[13,22]. Use of this framework will guide these analyses while recognizing their associated strengths and weaknesses. In turn, this will help stakeholders elucidate which method(s) for adjusting for treatment crossover might be most appropriate in a particular clinical trial scenario. The confidence in these methodologies to predict comparative effectiveness is increasing, and use of these should allow the effectiveness of new therapies to be better estimated, thereby leading to better clinical policy decision-making and improved population health.

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CONFLICT OF INTEREST

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TABLES

Table 1. Summary of time to crossover in VEG105192 (treatment-naive population, 15 March 2010 cutoff)

	Placebo (N = 78)
n	40
Minimum, months	2
1st quartile, months	4.6
Median, months	8.1
3rd quartile, months	13.8
Maximum, months	25

Table 2. Summary of final OS results for the treatment-naive population in VEG105192 (15 March 2010 cutoff)

Method of estimation	HR	95% CI
ITT analysis (log-rank)	1.01	0.72–1.42
ITT analysis (Cox regression)		
Unadjusted for baseline characteristics	1.027	0.728–1.447
Adjusted for baseline characteristics	0.859	0.602–1.223
Censoring on crossover	1.01	0.65–1.55
Censoring on crossover (Cox regression)		
Unadjusted for baseline characteristics	1.051	0.688–1.627
Adjusted for baseline characteristics	0.917	0.588–1.428
Censoring on crossover or receipt of post-study anticancer therapies (Cox regression)		
Unadjusted for baseline characteristics	0.797	0.493–1.289
Adjusted for baseline characteristics	0.640	0.390–1.049
Crossover as a time-dependent covariate (Cox regression)		
Unadjusted for baseline characteristics	1.075	0.696–1.661
Adjusted for baseline characteristics	0.941	0.607–1.459
IPCW (informative censoring defined as crossover to pazopanib or receipt of post-study anticancer treatment)		
Adjusted for baseline characteristics	0.642	0.266–1.248
RPSFT unweighted		
Unadjusted for baseline characteristics	NA	NA
Adjusted for baseline characteristics	0.310	0.073–1.715
RPSFT weighted (base-case)*		
Unadjusted	0.501	0.136–2.348
No post-study anticancer treatment (log-rank/Pike estimator)		
No post-study anticancer treatment irrespective of progression status	0.300	0.150–0.620
No post-study anticancer treatment, excluding patients still on study drug	0.380	0.200–0.720
Patients eligible for post-study anticancer treatment but declined	0.380	0.170–0.820

*The estimation procedure was weighted to account for the fact that more control group patients were receiving pazopanib than experimental group patients.

CI = confidence interval; HR = hazard ratio; IPCW = inverse probability of censoring weighted; ITT = intent to treat; OS = overall survival; RPSFT = rank-preserving structural failure time.

Table 3. Adjusted indirect comparison of pazopanib and sunitinib

	OS PAZ vs SUN, HR (95% CI)	Median OS, months (95% CI)
Adjusted indirect comparison using ITT HR 1.01 (PAZ vs BSC)	1.96 (not reported)	Not reported
Adjusted indirect comparison using RPSFT HR 0.501 (PAZ vs BSC)	0.97 (0.36–2.61)	PAZ: 27.8 (5.7–137.9) SUN: 26.8 (18.9–37.9)
COMPARZ study final OS data (PAZ vs SUN)	0.92 (0.79–1.06)	PAZ: 28.3 (26.0–35.5) SUN: 29.1 (25.4–33.1)

BSC = best supportive care; CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; PAZ = pazopanib; RPSFT = rank-preserving structural failure time; SUN = sunitinib.

FIGURE LEGENDS

Fig. 1. Percentage of patients originally randomized to VEG105192 receiving pazopanib, by treatment group and time since randomization (15 March 2010 cutoff).

Fig. 2. Kaplan-Meier curves of overall survival in VEG105192 (treatment-naive population, 15 March 2010 cutoff).