ADJUSTING FOR TREATMENT CROSSOVER IN A TRAMETINIB METASTATIC MELANOMA RCT: IDENTIFYING THE APPROPRIATE METHOD

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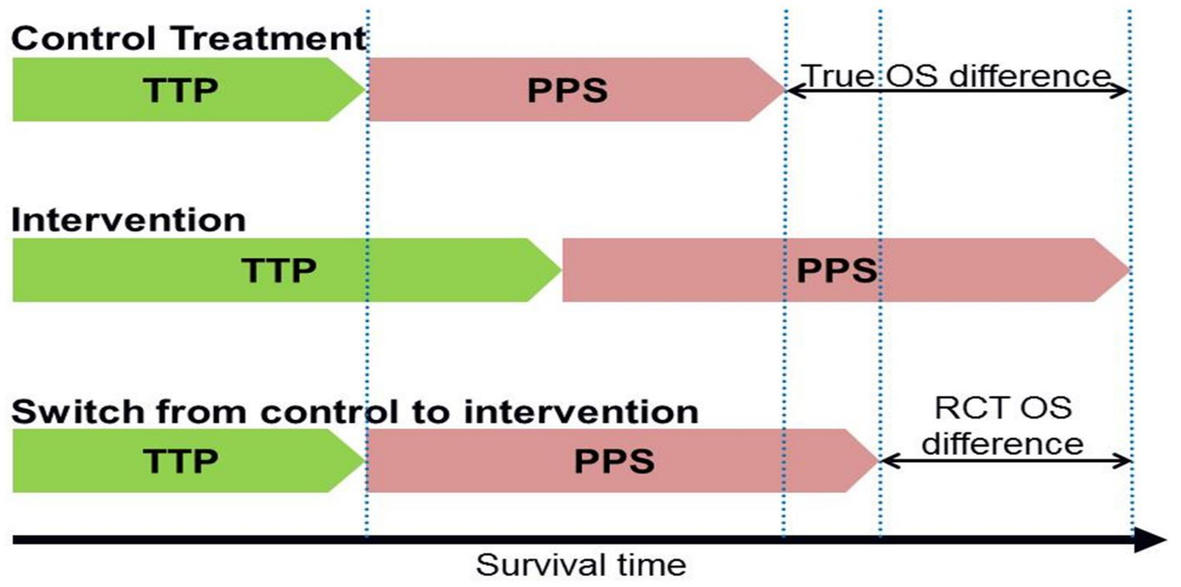
Objectives

Treatment crossover refers to the situation in randomised controlled trials (RCTs) where patients randomised to the control group switch to the experimental treatment. This leads to biased estimates of treatment effects if crossover is not appropriately controlled for. Several crossover adjustment methods are available, but previous research has shown that the optimal adjustment method depends upon the characteristics of the trial [1].

This study applies crossover adjustment methods to an RCT comparing trametinib to chemotherapy in patients with $BRAF^{V600E/K}$ mutation-positive advanced or metastatic melanoma (NCT01245062), and investigates which adjustment method best fits this case study. Patients enrolled in the METRIC clinical trial were randomised 2:1 to receive trametinib 2 mg once daily or chemotherapy (DTIC or paclitaxel). There were 273 patients in the primary efficacy population (trametinib, n = 178, chemotherapy, n = 95) and 64 (67.4%) chemotherapy control group patients switched onto the experimental treatment.

Figure 1: Treatment switching illustrated



OS, Overall survival; TTP, time-to-progression; PPS, post-progression survival; RCT, randomised controlled trial

Methods

RPSFTM & IPE ALGORITHM

The standard single parameter RPSFTM (Rank Preserving Structural Failure Time Model) and the IPE (Iterative Parameter Estimation) Algorithm split the observed event time, T_i, into time spent "on" treatment (T_{On_i}) and time spent "off" treatment (T_{Off_i}). Counterfactual event times, U_i, are calculated, and are related to observed event times with the following causal model:

$$U_i = T_{Off_i} + e^{\psi 0} T_{On_i}$$

Where $e^{-\psi 0}$ represents the acceleration factor associated with the intervention – the amount by which expected survival time is increased by treatment.

Key model requirements:

- Non-active (e.g. placebo) comparator
- Common treatment effect: The treatment effect of the experimental treatment is the same for switchers and experimental group patients, regardless of the disease stage at which it is received.

IPCW

The IPCW (Inverse Probability of Censoring Weights) involves censoring switchers at the time of treatment switch, and weighting remaining patients according to their similarity to switchers, using information on baseline and time-dependent covariates.

A weighted Cox regression model is utilised to estimate an adjusted hazard ratio. A weighted Kaplan-Meier curve can also be obtained.

Key model requirements:

- No unmeasured confounders: need data collected at baseline and over time on all variables that are prognostic of switching or survival
- E.g. patient choice as to whether to switch
- Correctly specified models for switching and survival

Two-stage methods

Two-stage methods involve using data on post-progression survival in the control group as an observational dataset, and estimating the treatment effect specific to switchers. Then, counterfactual survival times are estimated using:

$$U_i = T_{A_i} + \frac{T_{B_i}}{\mu_B}$$

Where T_{A_i} represents the time spent on control treatment, T_{B_i} represents the time spent on the new intervention and μ_B is the treatment effect (acceleration factor) in switching patients.

Key model requirements:

- No unmeasured confounders at the time of progression
- Switching must occur soon after progression

Results

Analysis	Description	HR			AF			CF HR comparison⁺	Median (chemo group, days)
		Point estimate	Lower 95% CI	Upper 95% CI	Point estimate	Lower 95% CI	Upper 95% CI		
1	Unadjusted GSK analysis (to provide a 'baseline' analysis)	0.72	0.52	1.01	-	-	-	-	338.0
8	IPE Algorithm 'treatment group' analysis	0.27	0.08	0.94	4.36	-	-	1.89	171.6
9	IPE Algorithm 'on treatment – observed' analysis	0.38	0.15	0.95	8.62	-	-	1.18	-
6	RPSFTM 'treatment group' analysis	0.38	0.15	0.95	1.95	1.03	3.41	1.00	220.0
7	RPSFTM 'on treatment – observed' analysis	0.37	0.14	0.95	7.00	1.06	-	0.96	-
6b	RPSFTM 'treatment group' analysis without recensoring	0.49	0.25	0.96	1.93	1.05	3.17	1.00	220.0
10	IPCW	0.48	0.25	0.91	-	-	-	-	
11	Two-stage Weibull	0.43	0.20	0.96	-	-	-	-	244.2
11b	Two-stage Weibull without recensoring ¥	0.53	0.29	0.97	-	-	-	-	244.2

Note: results using the preferred approach for each method are highlighted in red and the preferred method is indicated by ¥. Results are given to 2 decimal places. IPE AF confidence intervals not estimated as bootstrapping not conducted. IPE HR confidence intervals estimated through a test-based procedure, using p-value from the Weibull unadjusted analysis.

⁺The CF HR comparison represents the comparison of counterfactual survival times in each randomised group if *no* patients in either group received any treatment, given the treatment effect estimated by the method. Successful estimation would result in a CF HR of 1.00

- In the primary efficacy population, the unadjusted hazard ratio (HR) for overall survival (OS) was 0.72 (95% Confidence Interval 0.52 – 1.01) in the GSK analysis.
- Point-estimates of the adjusted HRs produced by the most plausible crossover adjustment methods ranged between 0.48 and 0.53, consistently favouring trametinib.
- In the first-line metastatic subgroup, the most suitable adjustment methods resulted in HR point estimates ranging from 0.44 to 0.55, compared with the unadjusted HR of 0.74 (95% CI 0.49 – 1.12) in the GSK analysis.
- The results were sensitive to the technique used to apply each method. Key issues included recensoring, the active nature of the comparator and the choice of covariates included in the analyses.

Conclusions

- Each of the crossover adjustment methods result in a lower HR than the unadjusted analysis, showing improved OS benefit of trametinib compared to chemotherapy.
- However, the crossover-adjusted results are dependent on key assumptions. It is important to analyse trial characteristics and model output carefully when identifying which applications of the adjustment methods are most plausible.
- RPSFTM and IPE methods require a non-active comparator, which is not ethically feasible in this case. They also rely on the common treatment effect assumption, which may be implausible if the capacity to benefit from treatment is reduced after disease progression. Tests of the data imply that there is no significant difference between pre- and post-progression treatment effects.
- The unmeasured confounders assumption is important for IPCW and two-stage methods, but convergence problems occurred for the IPCW due to the small sample size. Subsequently, some prognostic characteristics could not be included in the IPCW analysis.
- Recensoring of the data can be applied for the RPSFTM and two-stage method to reduce bias by breaking the dependence between censoring time and treatment; but in the METRIC trial, recensoring is considered inappropriate because it will exacerbate the bias arising from the changing treatment effect over time.

Reference

[1] Latimer NR, Abrams KR, Lambert PC, Crowther MJ, Wailoo AJ, Morden JP, Akehurst RL, Campbell MJ. Adjusting survival time estimates to account for treatment switching in randomized controlled trials – an economic evaluation context: Methods, limitations and recommendations. Med Decis Making, January 21, 2014

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