Comparing emerging drugs in metastatic Renal Cell Carcinoma (mRCC) without hazard ratios

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Background and objectives

• Comparing gain in survival from emerging treatments often has to rely on indirect comparison of treatments. Pivotal trials compare new treatments with an established one, be it placebo or standard of care. However, in rapidly-changing therapeutic landscapes, the most relevant comparator may not be available for introduction in these trials yet. Comparison between new, relevant treatments has thus to rely on network meta-analysis. Such comparison is especially of interest to payers and HTA bodies, who must weigh benefits of new drugs against each other, notably through the introduction of this comparison in cost-effectiveness models.

• Typical metrics used to compare survival data are hazard ratios (HR) and median survival times. Meta-analyses are therefore typically performed on HR values from recent pivotal trials. However, such comparisons rely on the assumption of proportional hazards between survival curves within each trial and require HR values to be available for each trial.

• We developed here an application of a more robust method to compare survival curves in absence of proportionality of HR or when no HR is available at all.

Method

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2. The resulting full survival curve comparing emerging treatments...
3. …constitutes a more accurate comparison of survival than in cost-effectiveness models.
4. …enables to report a valid HR for the indirect comparison of emerging treatments – since hazard ratios can vary with time.

Uses and Extensions of the Method

Two practical examples of a method to meta-analyse full survival curves (without relying on HR) are presented.

• In mRCC example traditional meta-analysis of overall survival HRs on the 2 studies would slightly favour cabozantinib: HR of .95 vs nivolumab, not significant

• However, the full picture of the overall survival benefits of these two treatments is poorly captured by this single metric.

• We notice that HR is a function of time (Figure 7). Median estimate of HR of nivolumab vs cabozantinib is greater than 1 for the first approx. 9 months (favouring cabozantinib), but after that it favours nivolumab.

• This difference is also reflected in Figure 6: estimate of OS is initially higher for cabozantinib, but after 12 months nivolumab has higher estimate of proportion of surviving patients.

• Therefore the method implemented here provides a more robust and complete way to describe differences between the two treatments.

• This approach has crucial impact on the credibility of CE:
  a. the baseline might be chosen from a study-arm that reflects best the real-life population/conditions of interest.
  b. all the other curves generated by the model are linked to the same settings, which allows to estimate the costs/effectiveness of all considered interventions in a more realistic way.

Discussion

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Conclusions

• Two cases, one simulated, one on very recent mRCC data, were presented in which a simple meta-analysis of HR was either impossible or not giving an accurate representation of the survival benefit conferred by the drug.

• Meta-analysing parameters of survival curves [1] is a solution to accurately compare treatments, and is especially relevant in rapidly changing treatment landscapes.

• Finally, meta-analysing not just the hazard ratio but all parameters of survival curves and adjusting them can allow to build a cost effectiveness model in a situation where comparisons based on HR or on median survivals are not available or not feasible.