Network meta-analysis with time-varying hazard: a comparative analysis of survival outcomes

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Introduction

- In oncology, the standard approach to network meta-analysis (NMA) of survival outcomes is based on hazard ratios (HRs) where treatment effect is assumed to be proportional over time.[1-3]
- In oncology trials, it is often observed that treatment effects may be multidimensional in nature, therefore HRs derived from trial data may not generate plausible long-term predictions of clinical efficacy[1-5], which in turn, may have a significant impact on decision-making when assessing the cost-effectiveness of therapies.
- Over the past few years, several authors have presented alternative analytical methods to overcome this limitation:
  - Treatment effects based on the scale and shape parameters of parametric survival curves.[3]
  - Multi-dimensional treatment effects with fractional polynomials (FP).[2]
  - Restricted cubic splines (RCS) models with baseline log-cumulative hazard.[1]

Objective

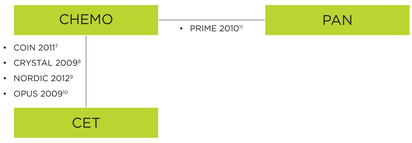
- To conduct NMA using alternative methodologies and compare results to understand how the selected methods might influence survival estimates.

Methods

Study selection

- In order to select randomised controlled trials (RCTs) for the NMA, we searched for a review from the Cochrane Database of Systematic Reviews due to the thoroughness of the approach and the high quality standards of these reviews.
- We identified a review of epidermal growth factor receptor (EGFR) inhibitors for metastatic colorectal cancer (mCRC), and selected studies that examined the use of EGFR inhibitors as a first-line treatment (in addition to standard of care) in KRAS exon 2 wild-type patients.[6]
- The network of evidence included in the analyses is presented in Figure 1.
- Median survival in the selected studies was between 18 and 25 months.

Figure 1: Network of evidence for OS mCRC



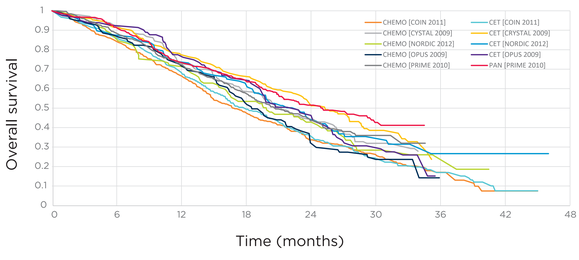
CET, cetuximab; CHEMO, chemotherapy; PAN, panitumumab.

Data extraction

Overview

- Progression-free survival (PFS) and overall survival (OS) HRs reported in the original publications were extracted from selected publications.
- The PFS and OS Kaplan-Meier (KM) curves available in the original publications were digitised and individual patient-level data (IPD) were reconstructed using the method described by Guyot *et al*.[7]
- Overall survival results across the selected studies are presented in Figure 2.

Figure 2: Survival of patients across different clinical trials



Statistical analysis

- **Model 1:** NMA based on proportional hazards assumption. Parametric survival distributions were fitted for all the CHEMO arms (reference treatment). The treatment effect, log HR, is assumed to follow a normally distributed likelihood and hence the identity link was used for our analysis.
- **Model 2:** NMA based on parametric survival curves. The Weibull distribution was selected, after which scale and shape for the reference treatment was obtained. The study-specific difference of the scale and the shape relative to treatment of interest was calculated to obtain the hazard functions for each treatment (i.e. CET and PAN).
- **Model 3:** NMA based on FPs. First- and second-order FPs were implemented with powers ranging from -2 to -1. The deviance information criterion (DIC) was used to compare goodness of fit of FPs with different powers.
- **Model 4:** NMA using RCS. Restricted cubic splines were used to model the log-cumulative hazard for each trial. For simplicity, only 1-knot (placed at 33% quartile of log-time) was selected. The function of the RCS was orthogonalised using the Gram-Schmidt process.
- **General considerations:**
  - Fixed-effects models were considered, assuming all studies were drawn from one population.
  - All the analyses were conducted in a Bayesian framework in WinBUGS, using the Markov Chain Monte Carlo method. The WinBUGS sampler, using three chains, was run for 50,000 iterations after the first 30,000 iterations were discarded (burn-in).
  - Convergence of the chains was confirmed by the Gelman-Rubin statistic.
  - The basic RCS function was obtained in R before the NMA was initiated in WinBUGS.

Results

- Only the details for the OS NMA are presented here (PFS not shown).
- In Model 1, Weibull proportional hazards model was selected based on the Akaike information criterion and Bayesian information criterion. The HR for CET vs CHEMO and PAN vs CHEMO was 1.02 [0.94 - 1.02; 95% CI] and 0.81 [0.65 - 1.00; 95% CI], respectively.
- The graphs for the hazard rates for Models 2 and 3 are presented in Figures 3 and 4, respectively. For Model 3, the second order FP with power 1=-0.5 and power 2=-0.5 was chosen as the best fitting model, based on DIC values. Both models indicated that the hazards for all treatment varies over time, but significant discrepancies were observed on the rate of hazards between the two models.
- The HRs over time for Model 2 and 3 are displayed in Figures 5 and 6, respectively. The models suggested the HRs may vary over time, but the results were not comparable between the two models. For instance, Model 2 showed a relatively constant HR for CET vs CHEMO, whereas Model 3 resulted in a HR that monotonically increases up to 9 months and then decreases.
- Model 4 yielded similar results to Model 3 (results not shown).
- The comparisons of median OS and long-term survival (i.e. proportion of patients alive at 40 months) across the four models are displayed in Figures 7 and 8, respectively.
  - The median OS was comparable across the four statistical models.
  - There was a substantial variation in long-term survival estimates across different models.

Figure 3: Network meta-analysis based on parametric survival curves (Model 2): hazard rate over time

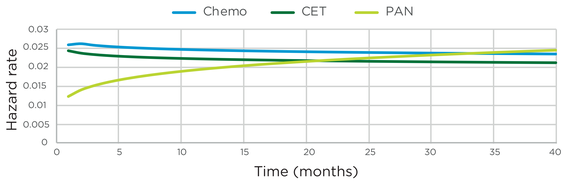


Figure 4: Network meta-analysis based on fractional polynomials (Model 3): hazard rate over time

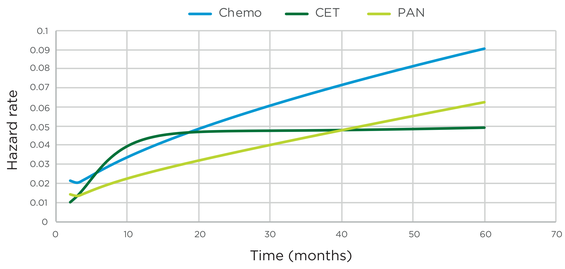


Figure 5: Network meta-analysis based on parametric survival curves (Model 2): hazard ratio over time

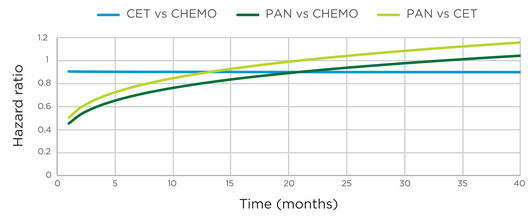


Figure 6: Network meta-analysis based on fractional polynomials (Model 3): hazard ratio over time

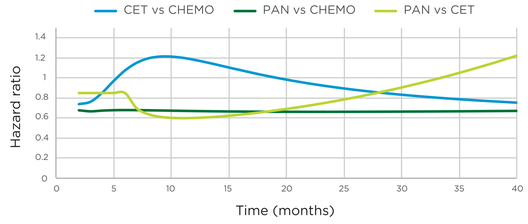


Figure 7: Median overall survival estimated with Models 1 to 4

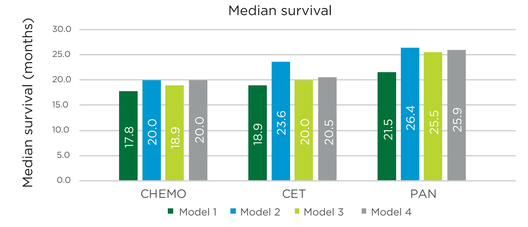
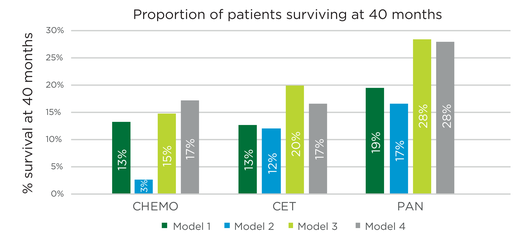


Figure 8: Estimated long-term survival with Models 1-4



Conclusions

- In the RCTs included in our analyses, treatment effects were multidimensional and the proportional hazard assumption was violated. Hence, the use of reported summary HRs from clinical trials for NMA is likely to bias the estimated treatment effects of therapies.
- Despite the use of advance analytical methods to handle multidimensional treatment effects over time, we observed that there are considerable discrepancies across different types of models.
- Only RCT data were used in our study; the use of real-world evidence to validate long-term projections of survival estimates from each of the different statistical models was beyond the scope of this analysis.

References

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