Cost-utility and expected value of perfect information related to trabectedin in the treatment of metastatic soft-tissue sarcoma: the publicly funded comments explored

I read with interest the comments by Blomqvist, Johansson and Tarkkanen [1] (later, the commentators). Three key issues had been misunderstood concerning the article [2], which reported the cost-effectiveness analysis (CEA) of trabectedin in the treatment of metastatic soft-tissue sarcoma (mSTS) after anthracycline/ifosfamide: means were mixed with medians [1], the CEA [2] followed the official Finnish setting and guidance for health economic evaluations [3] and the data presented [1] was not comparable/related to the CEA [2].

Ideally, survival times should be reported as exhaustive means together with Kaplan–Meier curves based on a large-enough randomized clinical trial, as this would enable an unbiased analysis of hazard ratios—the time-to-event summary statistic of choice [4]. However, most trials provide median survivals when all patients have not met the end points and the valid estimation of means based on the censored data could result in statistical modelling/estimation. While it is possible to carry out CEAs and indirect comparisons (ICs), including meta-analyses based on mean time-to-event data [5], medians are not a suitable basis for IC [4] or CEA.

Firstly, the commentators [1] mixed estimated means and censored medians, and Soini et al. [2] do not mention median anywhere. The claim ‚Äî the median survival benefit ‚Äî [1] is not from the CEA (for example [2] page 218 ‚Äî mean overall survival . . . ‚Äî). The expected value of continuous distribution is mean. The setting [3] appraises the use of expected values, and the costs and effectiveness should be reported in equivalent statistics. Thus, the mean survivals and mean costs were reported [2]. Sometimes, parametric survival models can be used to estimate the mean survivals [6]. Medians are problematic if a relatively large number of patients have not met the end points of interest or, especially, if the survival distribution related to different treatments is skewed in a different magnitude. Thus, and due to the uncertainty of IC, linear interpolation with 20% cut-off was used to estimate the mean survivals (compare Appendix 1 in [2]).

Secondly, the CEA [2] was carried out during the latter part of 2008 and followed the official setting [3], which appraises comparison against the labelled/evident treatments. The postulated comparison against gemcitabine + docetaxel [1] seems implausible based on the studies found in the PubMed in 2008 and March 2011. In 2008, the scientific evidence/labelling/authorization of gemcitabine + docetaxel in mSTS was not established. Still the efficacy evidence of gemcitabine + docetaxel is controversial [7], there can be number of safety issues, the reported trials are small/narrow/heterogeneous/enriched/multiple-line studies, and the patient populations [7–10] are far from comparable to the patients in the CEA [2]. Research will show how the treatments perform [11].

Finally, the commentators state that the data [1] given in the background of the article [2] raise issues. However, none of the points they [1] make have any impact on the CEA results [2]. If anything, their mixing references [1] with different base populations raise issues. For example, the results [12] referred to [1] only apply for resectable/local extremity-STS and not to the base population of our CEA [2]: the commentators [1] exclude some 41% (597 versus 1013 [12]) of the extremity-STS patients (with the highest risk for metastasis). Furthermore, the growth rates [1] apply to pulmonary/lung metastases and are mainly from the 1980s. I agree that stable disease (SD) may be hard to capture. However, SD and progression states had an equivalent quality of life (EuroQoL 5D, 15D, Short Form 6D) value and the equivalent monthly costs after the comparator drugs had been administered [2]: the exclusion of SD would
not change the primary results. To sum up, the publicly funded comments ([1] compare [13] page 2) raised some of the common issues [6, 14–17].

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