Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Institute for Quality and Efficiency in Health Care

IQWiG in dialogue 2014

"Benefit assessment in studies with allowed treatment switching"

Abstracts of presentations

Professor Dr Daniel Strech, Hanover Medical School (MHH)

The ethical dimensions of studies with allowed treatment switching

The ethical dimensions of studies with allowed treatment switching will be illustrated by specifying various principles of an internationally established framework in research ethics for this issue. The following seven principles will be specified in the presentation: 1) social value, 2) scientific validity, 3) fair selection of study participants, 4) advantageous risk-benefit ratio, 5) independent review, 6) informed consent, and 7) respect for the study participants. Based on this specification and clarification of ethically relevant principles, an approximate assessment will be given of the reasons for and against studies with allowed treatment switching as well as the alternative study designs available.

Professor Dr Bernhard Wörmann, German Society of Haematology and Oncology (DGHO)

Criteria for treatment switching in oncological studies

In many oncological indications, nowadays more than one effective treatment option exists for the specific situation. This is true both for treatment concepts with a curative and for those with a palliative purpose. The treatment chosen in each case is not a singular measure, but an element of a sequential therapy.

The concept of sequential therapies also concerns the treatment of patients in clinical studies. Subsequent therapies in patients with disease progression or recurrence may particularly influence the outcome “overall survival”. A crossover design is a special case. Under defined conditions, patients in this model can be treated according to the other treatment arm. The crossover design is based on ethical considerations. How much influence the crossover has on the outcome depends on the number of patients affected and on the strength of the effect.

The subsequent use of other drugs with an antineoplastic effect during the further course of disease is also relevant for the evaluation of the final results of a study. This concerns both survival time as well as potentially adverse events and patients’ quality of life.

Since nowadays sequential therapy is more the rule than the exception in oncology, its conceptual integration into the study design, methodological approaches for calculating the benefit of individual interventions, and long-term documentation of study patients are required.

PD Dr Thomas Sudhop (BfArM)

The role of BfArM in the planning, authorization and acceptance of clinical studies and their results in oncology

Because of the variety of tasks and services the Federal Institute for Drugs and Medical Devices (BfArM) offers, it often accompanies the development of new drugs at a very early stage before the approval. BfArM may be involved both in the area of scientific consultation and in the area of authorization of clinical studies, and may also adopt different roles.
The approval is usually the focus of the scientific consultation. Particularly in oncological studies, the choice of outcomes, the most suitable population, and the comparator therapy are the most important topics of discussion. In the area of authorization of individual clinical studies, freedom of research and regulatory restrictions compete with each other; both have to be adequately considered by BfArM. This sometimes leads to the problem that BfArM has to treat a clinical study differently from the authorization perspective than would be ideal from the approval perspective. These problems particularly occur when new therapeutic options challenging the choice of the comparator therapy become available in the course of a development programme. This comparator therapy might still have been considered appropriate in the scientific consultation by the regulatory authorities. In those cases, either the comparator therapy chosen has to be generally reconsidered or mechanisms need to be stipulated allowing the patients to switch to a treatment that may be better for them. This problem exists in placebo-controlled studies as well as in oncological studies in which the comparator treatment is approved, but based on relatively old data and whose status as standard treatment has been challenged by more recent study results. Whereas, from the approval perspective, the switching of patients between treatment groups should be strictly avoided methodologically, this may suddenly be ethically required from the perspective of the authorization of a specific clinical study. Study data showing a clear advantage of a new treatment over an established standard treatment principally call into question the use of the established standard treatment in other studies, as this would violate the Declaration of Helsinki requirement for a comparison with the “best proven intervention”. However, this would only be ethically acceptable if it was ensured at the same time that the patients in such a situation would not be subject to the risk of additional or irreversible damage, a situation that is unfortunately too common, particularly in oncology.

Dr Volker Vervölgyi, Lars Beckmann (IQWiG)

Evaluation of treatment switching in the Institute's assessments

In oncological studies, treatment switching is often possible in the course of the study, for example from the control treatment to the new treatment. This is usually done after (radiological) progression of the disease. Treatment switching after progression can lead to bias of the result for outcomes that occur after progression (e.g. overall survival). Also against the background that this bias can occur both in favour and to the disadvantage of the new treatment, treatment switching may lead to the situation that the results can no longer be interpreted in a meaningful way. Different methods are proposed in the literature aimed at considering treatment switching in the analysis to reduce the influence of bias. These methods are mainly summarized in the work of Morden et al. (*BMC Med. Res. Methodol.*, 2011), which also investigated their characteristics in simulation studies.

This presentation will explain the way the Institute has handled this problem so far, using examples from dossier assessments that included studies with treatment switching. Moreover, it will describe whether one of the methods on the handling of treatment switching proposed in the literature was used in these examples and, if so, whether the underlying assumptions were checked and discussed as far as possible.

Dr Norbert Holländer (Novartis)

Methods to estimate survival time after treatment switching in oncology – overview and practical considerations

Many oncological phase 3 studies use progression-free survival (PFS) as a primary outcome and overall survival (OS) as a secondary outcome. There are often no further treatment options in very advanced cancer; patients in the control arm receive placebo. Since randomization to placebo still remains difficult with regard to the feasibility of a cancer study, some studies allow switching to the new active treatment after tumour progression is observed and documented. Whereas this does not influence the primary outcome "PFS", its influence on the OS analysis is very likely. Placebo patients who switch to the active treatment might benefit from the delayed treatment, so that the intention to treat analysis does not reflect the "true" difference in OS between the new treatment and placebo. The presentation provides an overview of the different statistical methods that consider treatment switching and thus aim to conduct an adjusted OS analysis. Similarly to the article by Watkins et al. (1), specific assumptions, as well as advantages and disadvantages of all methods described, are pointed out. Moreover, the use of the rank-preserving structural failure time (RPSFT) model and of inverse probability of censoring weights (IPCW) are illustrated with a clinical study, and various practical aspects of these two methods are discussed (2,3).

References

1. Watkins C, Huang X, Latimer N, Tang Y, and Wright EJ: Adjusting overall survival for treatment switches: Commonly used methods and practical application. *Pharmaceutical Statistics* 2013; 12(6): 348-57.
2. Korhonen P, Zuber E, Branson M, Hollaender N, Yateman N, Katiskalahti T, Lebwohl D, and Haas T: Correcting overall survival for the impact of crossover via a rank-preserving structural failure time (RPSFT) model in the RECORD-1 trial of everolimus in metastatic renal-cell carcinoma. *Journal of Biopharmaceutical Statistics* 2012; 22(6): 1258-1271.
3. Korhonen P, Malangone E, Sherman S, Casciano R, Motzer RJ, Baladi J, Haas T, Zuber E, Hollaender N, and Lebwohl D: Overall survival of metastatic renal cell carcinoma patients corrected for crossover using inverse probability of censoring weights and rank-preserving structural failure time models: Two analyses from the RECORD-1 trial. *2010 ASCO Annual Meeting, June 4 – 8, 2010, Chicago, IL*, Abstract #4595, Poster Presentation.

Professor Dr Ulrich Mansmann, Ludwig Maximilians University (LMU) Munich

Adjustment of overall survival (OS) after crossover – aspects from the perspective of the benefit assessment –

Crossover of treatments for patients with advanced tumours in oncological phase 3 studies is indicated for ethical and practical reasons. Treatment switching is more problematic for the benefit assessment of treatments than for their approval. Treatment switching leads to a conceptual divergence between what is exactly investigated in an RCT and what is required in a benefit analysis: The control arm is contaminated by the switching. It would be useful for the benefit assessment to adjust the estimates of OS with regard to the treatment switching, and to exclude the consequences of the treatment switching. The presentation considers limitations and prerequisites of the most important adjustment methods and their relevance for consideration in a benefit assessment. It is obvious that different methods are based on different assumptions and follow different methodological principles. They are therefore likely also to produce different results. Practical and theoretical problems will be discussed and an analysis framework by Latimer et al. (2014) will be referred to, which offers rational guidance for the unbiased effect estimate and its sensitivity analysis.

References

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