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Ao.Univ.-Prof. Dr. W. Hilbe

Changing paradigms in clinical trials

W. Hilbe

Department of Internal Medicine V, Hematology and Oncology, Medical University Innsbruck, Innsbruck, Austria

Clinical trials are necessary to find out whether promising approaches to cancer prevention, diagnosis, and treatment are safe and effective. There are different types of clinical trials which comprise treatment trials, prevention trials, screening trials or quality-of-life-trials (for details see: www.cancer.gov). In general, clinical research follows a series of phases (I–IV), which guarantees the most reliable information about the investigational drug and protects the patients.

From a traditional point of view, studies with a significant survival (OS) benefit have been considered as a positive trial and the pharmaceutical industry has succeeded to get approval for new drugs by the regulatory authorities even if the significant results had been of minor clinical relevance [1].

Presently we are faced with a profound change in approval policy, which could have substantial implications on the way clinical trials will have to be designed in the future. This is explained by two decisions of the European Medicines Agency (EMEA) in 2009, both concerning non-small cell lung cancer (NSCLC).

The EMEA granted marketing authorisation for gefitinib for NSCLC patients with activating mutations of EGFR-tyrosine kinase in all lines of therapy. The licence was based on the data of two pivotal phase III studies, the IPASS and the INTEREST trials [2, 3]. In the IPASS trial, gefitinib significantly delayed progression-free survival (PFS) and improved response rates (RR) in NSCLC patients with the activating mutation of EGFR-TK compared to standard doublet chemotherapy [2]. However, data on overall survival were not available. In the INTEREST trial, gefitinib demonstrated equivalent survival after chemotherapy for unselected patients who progressed on or after chemotherapy. In both trials gefitinib demonstrated a better tolerability profile and quality of life benefit compared to chemotherapy. Traditionally, the new drug might have succeeded to be approved in the second line setting and in unselected patients only because it was equivalent in OS and better concerning tolerability when compared with the standard procedure. First line approval in selected patients would have been postponed until survival data were available.

Secondly, the Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion, recommending the refusal of a change to the marketing authorisation for the medicinal product Erbitux concerning an extension of indication to non-small cell lung cancer (www.ema.europa.eu/humandocs/PDFs/EPAR/erbitux/Erbitux_Q&A_46951509en.pdf). The committee was concerned that the benefits were modest in terms of survival times, and that the "medicine did not have a convincing effect on how long patients lived without their cancer getting worse". Severe side effects were seen in some lung cancer patients who received Erbitux. In that study 1125 patients were randomly assigned to chemotherapy plus cetuximab ($n=557$) or chemotherapy alone ($n=568$) [4]. The study succeeded in reaching its endpoint and proved a significant OS benefit in the combination arm (median 11.3 months *vs.* 10.1 months; hazard ratio for death 0.871 [95% CI: 0.762–0.996]; $p=0.044$). PFS did not improve but the authors noted different censoring patterns in the two treatment groups. Additionally, analysis of time-to-treatment failure (TTF) showed a significant benefit in favour of chemotherapy plus cetuximab. From a historical perspective such a study would have been approved.

What are the consequences of these decisions facing a growing number of medicinal drugs aiming for approval and market access?

- We need substances that are effective and lead to a "clinically relevant improvement" of therapies. Secondly, new drugs should not increase toxicity compromising patients' quality of life. The reaction of the pharmaceutical industry is that inclusion and exclusion criteria of clinical trials are much more shaped to optimize results. This could lead to the point that these drugs can only be applied to a minority of patients. Facing financial restrictions of the medical system, the use of new drugs might be limited to their approved indications so that the benefit of this strategy for the community should be questioned. The ideal concept to optimize therapies would be to include biomarkers, which are highly predictive. This concept, however, is limited by the fact that for most of the new drugs biomarkers established in early drug development (mice, Phases I and II) failed their validity in the clinical human setting [5, 6]. In the present issue of *memo* Pircher et al. [7] discuss this topic for anti-angiogenic drugs and conclude: "*However, at the moment one universal biomarker does not exist and every anti-angiogenic therapy and every cancer type should be considered separately. The integration of biomarker assessment and validation can only succeed when we intensify*

Correspondence: W. Hilbe, MD, Department of Internal Medicine V, Hematology and Oncology, Medical University Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria.
E-mail: wolfgang.hilbe@i-med.ac.at

basic science and design clinical studies integrating meaningful biomarker programs." So we face an absolute discrepancy: We need biomarkers but we also need to test their validity in patients. Therefore, we can hardly select patients based on these biomarkers for their approval. It takes years to establish relevant biomarkers and to bring them into daily routine (her2 for herceptin) [8].

- The confusion about the adequate endpoint in clinical trials is perfect. Should we accept PFS and RR or should we insist on the "gold standard" OS? From the patients' view either a prolongation of life or an improvement of quality of life is relevant. The absolute amount of remission (more or less than 30% of the diameters according to RECIST criteria) and the duration of these remissions might be of minor relevance for the patient. On the other side we have to face the fact that there is a lack of standardized survival endpoint definitions [9]. The relevance of various clinical endpoints is discussed by M. Fridrik in the present issue of *memo* [10].
- The CHMP clearly weighted the benefits against the toxicity of new therapeutic concepts. So, for future studies inclusion of quality of life evaluations is strongly recommended.

If we are asked to design intelligent protocols of clinical trials, we are facing many open questions: which endpoint, which biomarker, which patients etc. In my opinion, the only realistic way to manage this challenge is to design "hypothesis generating" phase II protocols including translational research for the identification of biomarkers and to go on to phase III studies only if a clinically relevant benefit can be expected. Additionally, there are reasonable arguments in favour of the need of randomisation in phase II trials, ideally with blinding and dose-ranging [11], which could enable greater clarity of phase II results. This would reduce potential bias from inter-trial variability if historical controls were utilized. The present development will certainly change the strategies for the design of clinical trials and hopefully will lead to more efficacious drugs for our patients.

Conflict of interest
The author has acted as a consultant, taken part in formal advisory activities, and received grant support and honoraria from AstraZeneca, Merck and Roche.

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