Ethics of umbrella and basket trials in precision oncology

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Authors' contribution:
A. Study design/planning • B. Data collection/entry • C. Data analysis/statistics • D. Data interpretation • E. Preparation of manuscript • F. Literature analysis/search • G. Funds collection

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To the Editor,

the project *Ethics of research with human subjects in precision medicine* funded by the National Science Centre in Poland concerns a new approach in treating clinical trial participants by tailoring appropriate therapy to the molecular targets within the patient's disease. The aim of the project is to perform theoretical and ethical analyses of novel research designs in precision oncology, umbrella trials, and basket trials, in the context of 7 fundamental ethical requirements of conducting research with human participants: 1) social or scientific value, 2) scientific validity, 3) fair subject selection, 4) favourable risk-benefit ratio, 5) independent review, 6) informed consent, and 7) respect for potential and enrolled subjects. The project applies evidence-based medicine and evidence-based ethics methodology to provide necessary information for making decisions in medicine and health care. The results of the project may contribute to the current debate on the ethical aspects of the research in precision medicine.

The first findings can be found in the article *Risk and benefit for umbrella trials in oncology: a systematic review and meta-analysis* published in BMC Medicine (2022) [1]. The article considers a favourable risk-benefit ratio criterion, which is met when the risk for participants is minimized, the expected benefits are maximized, and the benefits to trial participants and society outweigh or are proportional to the risks associated with participation in the research study [2]. This ethical requirement is particularly important in umbrella trials, which are considered to maximize direct health benefits to trial participants by dividing cancer patients into groups that will most likely respond to a given therapy [3, 4]. Within an umbrella trial multiple drugs matched to different molecular changes in one cancer type can be evaluated simultaneously in parallel sub-studies or cohorts [5]. Thus, we may expect better risk-benefit balance in umbrella trials than in classical trial designs.

To assess the overall benefit and risk in umbrella cancer trials my colleagues and I systematically searched for umbrella trials published between 1 January 2006 and 7 October 2019. Of the 6207 records screened, 31 sub-trials or arms of 9 umbrella trials enrolling 1637 patients were included in the analyses. We measured the benefit by the objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The overall ORR was 17.7%, the median PFS was 2.4 months, and the median OS was 7.1 months. We observed a significant difference in ORR between therapy types (13.3% for targeted therapies vs. 39.0% for a combination of targeted therapy and chemotherapy). We calculated the risk by the proportion of participants experiencing grade 3, 4, or 5 drug-related adverse events (AEs). The average drug-related grade 3/4 AE rate per person was 0.45, and the drug-related grade 5 AEs rate was 0.8%.

We compared these results to other studies analysing risk and benefit in classical trial designs and found that the ORR and AE rates were similar. Our findings do not support the expectation of increased patient benefit in umbrella trials in precision oncology. Further analyses of the ethical aspects of umbrella and basket trials are ongoing.

Disclosure

The author declares no conflict of interest.

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