SUMMARY

Introduction:

Cancer is the leading cause of death worldwide. Nearly 10 million people died of cancer in 2020 and it is estimated that the number of cancer deaths will continue to increase.

Despite huge financial outlays for the development of new anticancer drugs the likelihood of approval for oncology drugs is one of the lowest compared to other therapeutic areas.

New models of clinical trials have been designed to optimize and accelerate the process of bringing a new pharmaceutical drug to the market. The examples of such models are basket and umbrella trials which enable testing simultaneously several medicinal products.

The development of new drugs relates to specific ethical aspects. One of the important ethical requirements of conducting clinical trials is a favorable risk-benefit ratio which is met when: 1) the risk for trial participants is minimized, 2) the expected benefits are maximized, and 3) the possible benefits to participants and society outweigh or are proportional to the risk of participating in the trial.

One of the methods to maximize benefits and minimize risk in Phase I oncology clinical trials is to delay the recruitment of children by including only adult participants in the initial stages of clinical trials. Yet, no ethical analyzes that systematically assess the risk and potential benefits in Phase I clinical trials in pediatric oncology have been performed. In addition, the risk and benefit in basket and umbrella research designs have not been discussed. In the light of the dynamic development of oncology clinical trials, analyzes that critically assess the risk and benefits in clinical trials in oncology are urgently needed.

Aims:

The aims of the research work as part of the doctoral dissertation were: 1) systematic risk and benefit assessment in selected clinical trials in pediatric oncology and 2) analysis of risk and benefit in basket and umbrella clinical trials based on real examples.

Methods:

The research work was divided in two parts. The first part was meta-research based on the systematic review methodology. The second part consisted of theoretical analyzes.

Clinical trials meeting the inclusion criteria were included in the meta-studies. Risk was measured using serious, life-threatening or fatal treatment-related adverse events. Benefit for clinical trial participants was defined as a partial or complete response to tested therapy. Various statistical tools were used to analyze collected data such as: I^2 statistics, REML (restricted maximum likelihood), Q test, meta-regression or meta-analysis.

Theoretical analyzes describe current ethical issues and propose innovative solutions aimed at minimizing the risk and increasing the probability of benefit in clinical trials in oncology.

Results:

The pooled benefit in Phase I clinical trials in pediatric oncology (published between 2004-2015) was 10.3%. The highest risk (defined as death due to drug-related adverse events) was 2.1%. No difference was observed in the level of risk and benefit between Phase I oncology clinical trials in children compared to similar studies in adults. Furthermore, there was no difference in the level of benefit in Phase I studies recruiting additional group of participants within dose expansion cohort (DEC) compared to similar studies without DEC.

It was noted that the majority of Phase I clinical trials in pediatric oncology reported benefit data (167 out of 170 studies, 98%) whereas more than half of the studies (100 trials, 59%) reported no information on drug-related deaths. Despite the standards of reporting adverse events, part of the analyzed Phase I studies did not provide clear and complete information on the toxicity of tested drugs.

The pooled response rate in Phase II clinical trials in pediatric oncology testing targeted therapies (published between 2015-2020) was 24.4%. The overall drug-related death rate due to adverse events was 1.6%. When these results were compared to the first meta-research of Phase I clinical trials, the direct benefit for targeted therapies appeared to be higher in Phase II clinical trials (24.2%) than in Phase I clinical trials (3.5%). However, there was no difference in the treatment-related deaths between Phase I trials (1.8%) and Phase II trials (1.6%).

The analysis of risk and benefits in novel clinical trial designs showed that the results of basket and umbrella studies can contribute to a significant increase in knowledge about the nature and complexity of cancer. Nevertheless, the direct health benefit for the participants in these studies is limited and is based mainly on surrogate endpoints. The risk in these studies is, among others, related to the heterogeneity of malignancies. Patients are assigned to one of the many drugs tested based on a biopsy sample which may not reflect all genetic changes in the entire tumor. Consequently, patients may be assigned to the wrong therapy.

Therapeutic misconception and therapeutic misestimation are important problems in basket and umbrella studies. They are related to the requirement of obtaining informed consent from the potential participant. In the era of precision medicine and personalized therapies, clinical trial participants can believe and expect that all treatments are tailored not only to their disease but also to their own needs and preferences. In addition, patients may overestimate the possible benefits of participating in the study and underestimate the risk.

Conclusions:

The results showed that delaying the recruitment of children in Phase I clinical trials in oncology dose not translate to increased benefit and reduced risk compared to clinical trials with adults. Moreover, in pediatric oncology clinical trials testing targeted therapies there is no

difference in the level of drug-related death rate between Phase I and Phase II trials. Nevertheless, Phase II studies demonstrated a significantly higher benefit than similar Phase I studies.

Efforts should be made to minimize the risk of therapeutic misconception and therapeutic misestimation in basket and umbrella trials. Ethical challenges in these clinical trial models should be further discussed.