Current status and future perspectives of precision oncology in Greece

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Background

Cancer is the leading cause of death in Greece with over 64,000 cases reported annually and severe pain as one of the subsequent side effects. Multiple strategies, including the Maximum Tolerated Dose (MTD) approach, have been proven insufficient for the selection of cytotoxic agents, with wider therapeutic index and fewer off-target side effects. In contrast, the Project Optimus and the implementation of a pre-emptive 12-gene pharmacogenetic panel, prove to be an effective strategy for treatment selection.

Methods

Project Optimus, which was launched by FDA in 2021, is an initiative to transform the dose optimization process. During the clinical development phase, PGx-guided, PK-guided and PD-guided approaches could provide information about the dose-response relationship as well as the effect of the drug in patients with rare genotypes, during the post marketing phase. In addition, during the 12-gene PGx multicenter crossover study (NCT03093818), participants were genotyped for 50 germline variants in 12 genes and those with actionable variants received DPWG recommendations, with a follow-up of at least 3 months.

Discussion

The importance of dose optimization is prominent in the case of TKIs and mAbs. Studies on TKIs report that nearly half of the patients require dose reduction. Therefore, shifting away from the MTD approach allows the selection of the minimum effective and safe dose. It is estimated that the implementation of PGx guided drug and dose selection will reduce clinically relevant ADRs by 30% (ranging from 4% to 2.8%).

Conclusion

Drug-gene interactions identified during early phase clinical development may allow dose modification according to genotype to optimize exposure and reduce toxicities like those observed with DPYD, NUDT15, TPMT, and UGT1A1 in the post-marketing setting. Pre-emptive genotyping is another step to reducing clinically relevant ADRs within the European healthcare system, as indicated by the health centers in 7 European countries.

Objective

The aim of project Optimus is to identify the role of pharmacological tools such as pharmacogenomics, therapeutic drug monitoring, and pharmacodynamics, which could be integrated in the drug discovery process and influence clinical decision-making. Similarly, the aim of the 12-gene PGx study is to minimize the presence of treatment-related side effects and subsequently ensure treatment safety.

Graphic