Pediatric hematology: the cost of cure of childhood malignancies - Section 2

Deciphering (genetic) variation of early and late effects from childhood cancer therapies - overview of recent developments

Bruce Carleton

BC Children's Hospital, University of British Columbia, Vancouver, Canada

Adverse effects of chemotherapy are being increasingly recognized as important endpoints to consider in pediatric oncology besides cure. New studies have provided evidence of the unintended consequences of chemotherapy on major organ systems.[1] Serious toxicities have now been identified by several studies that include clinical as well as genomic determinants of late effects.[2-5] These include pharmacogenomic biomarkers which are increasingly understood. This is useful for predicting harmful outcomes and therefore for future clinical decision making.[2,3,6,7] Replication and validation of such findings in independent cohorts are critical in such pharmacogenomic studies.[8-10]

The number of clinical practice guidelines for the use of pharmacogenomic information is rapidly increasing. Guidelines for carbamazepine, codeine, warfarin and other drugs have been published. In particular, the Clinical Pharmacogenetics Implementation Consortium (CPIC) continues to publish peer-reviewed guidelines in Clinical Pharmacology and Therapeutics to assist implementation of pharmacogenomic testing into clinical practice.[11]

Figure 1. The Canadian Pharmacogenomics Network for Drug Safety wheel model for developing pharmacogenomic solutions to drug safety problems.

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For instance, guidelines for TPMT testing in patients receiving thiopurines have been written and recently updated.12 Systematic reviews of evidence and guidelines for the use of pharmacogenomics to predict cisplatin-induced ototoxicty and for anthracycline-induced cardiotoxicity are now available (Aminkeng F. *et al*., *unpublished,* 2016).[13]

Better approaches to replicating pharmacogenetic discoveries are needed. Bissell's recent paper in Nature describes the process that is needed and the difficulties with this branch of scientific process. Such studies will improve our understanding of when pharmacogenetics studies are most relevant and in which patients. Also, knowledge on what overriding factors negate the value of these genes in patient care is important to retrieve.[14] Finally, it is important to develop programs of gene discovery that include replication, validation of findings, translation into practice and robust commercialization, such that valid results can be used to design predictive models of drug harm that can be applied to survivor care (Figure 1).

References

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This paper discusses the limitations and risks of efforts to replicate genetic findings based on published literature as the methodological source from which replication is conducted.