Annals of Urological Research

Editorial
Published: 11 Jul, 2017

Improving Testicular Cancer Pharmacotherapy Through the Use of Pharmacogenomic Approaches

*Luis A Quiñones**

Department of Basic and Clinical Oncology, University of Chile, Chile

Background

Testicular cancer (TCa) is the most common cancer in young adult men with a mortality ratio of 0.3/100,000 inhabitants. It represents 1% of male neoplasms and 5% of urological tumors, with 3-10 new cases occurring per 100,000 males/per year. The most common subtypes of TCa are seminoma and non-seminoma germ cell. Seminoma TCa represents about 30% to 40% and non-seminoma rises to 50% to 60% of total TCa, and can be classified into embryo carcinoma, vitelin sack tumor, teratoma and coriocarcinoma [1,2].

In every case of TCa, surgery is the initial treatment (inguinal orchiectomy). After that, usually the eligible treatment is chemotherapy with combinations of bleomycin, etoposide and cisplatin (bleomycin/etoposide/cisplatin (BEP) or etoposide/cysplatin (EP)), used as the front line treatment, depending on histology and risk. In the second line, a PIV (cisplatin, ifosfamide and vinblastine) scheme is usually used. These are quite successful treatments for patients with seminoma (all stages combined) and the cure rate exceeds 95% of the treated cases [2,3]. Despite the high cure rates, chemotherapy is a complicated topic, due to the high possibilities of presenting serious adverse effects. Historical studies have reported the following side-effects for antineoplastic chemotherapy used in TCa: nausea/vomit secondary malign neoplasms and leukemia, cardiovascular diseases, peripheral neurotoxicity, ototoxicity, nephrotoxicity, lung toxicity, hipogonadism, decreased fertility, psicosocial disorders and cognitive damage. While peripheral neurotoxicity can be produced by several drugs, ototoxicity is produced mainly by cisplatin [4]. Moreover, chemotherapy used for TCa treatment often causes myelosupression, giving rise to febrile neutropenia, hemorrhage and anemia (60%), where the risk of febrile neutropenia is around 5% to 25% after 3 cycles to 4 cycles of BEP or EP [5-7].

Inter-individual variations of chemotherapy drug-response can be partially explained by genetic variations in pharmacokinetic and/or pharmacodynamic factors, and raise a substantial clinical problem. On this regard, a drug that is well tolerated and causes a positive response in some patients may be ineffective, toxic or cause adverse drug reactions in others. Pharmacokinetic factors influence plasma and tissue drug concentrations while pharmacodynamic factors modify drug sensibility, conducting to higher or lower effects than expected due to influence in the presence of receptors or other pharmacological targets. Thus, response to chemotherapy of TCa (efficacy and safety) may be partly determined by gene polymorphisms involved in the pharmacology of cytotoxic drugs used in the treatment of TCa.

In this sense, pharmacogenomic research on TCa has been mainly focused on enzymes that control the metabolism, uptake and response to many clinically used drugs, including bleomicin, etoposide and platins. Therefore, considering that most of the antineoplastic drugs are metabolized by Cytochrome P450, and that variant alleles in these enzymes commonly affect drug effectiveness [8,9]. The study of these phase I and also phase II enzymes should be properly addressed, in order to contribute to clinically more effective treatments.

On the other hand, cancer`s therapy effectiveness depends partially on the ability of cancer cells to repair their DNA, therefore less active DNA-repairing enzymes in cancer cells may lead to an improve in response to chemotherapy. Conversely, a tumor process can be initiated, when normal cells present impaired capacity to repair DNA. Considering the aforementioned, several pharmacogenomic studies in some of the about 130 genes of DNA-repair enzymes have consistently demonstrated positive correlations between SNPs and differential cancer treatment outcomes [10-12]. Over these studies, it has been demonstrated that polymorphisms more related to clinical response in DNA reparation enzymes and cancer patient's outcomes are XPD Asp312Asn (rs

OPEN ACCESS

Correspondence:
Luis A Quiñones, Laboratory of Chemical Carcinogenesis and Pharmacogenetics, Department of Basic and Clinical Oncology, Faculty of Medicine, University of Chile, P.O. Box 70.111, Santiago, Chile, Tel: (562) 29770741-29770744; E-mail: lquinone@med.uchile.cl

Received Date: *27 Jun 2017*
Accepted Date: *03 Jul 2017*
Published Date: *11 Jul 2017*

Citation:
Quiñones LA. Improving Testicular Cancer Pharmacotherapy Through the Use of Pharmacogenomic Approaches. Ann Urol Res. 2017; 1(1): 1004.

1799793), XPD Lys751Gln (rs 13181), ERCC1 8092C/A (rs 3212986) and ERCC1 118C/T (rs11615) [13].

Considering that BEP scheme is the world wide's most used pharmacotherapeutic treatment for TCa, it is of great importance to focus new research programs on understanding inter-individual response to these drugs using the pharmacogenomic approach.

BEP Drugs

Etoposide is a plant alkaloid that inhibits topoisomerase II in the process of DNA synthesis; it has been successfully used as an anticancer drug in chemotherapy. Etoposide is cell cycle dependent and phase specific, affecting mainly the S and G2 phases. High concentrations of etoposide (> 10 μg/mL) produce lysis of cells incoming mitosis and a lower number of cells appear to be stopped on going into prophase [14]. The main macromolecular effect of etoposide is the breakage of DNA strands through DNA topoisomerase II inhibition and formation of reactive oxygen species [15]. It is known that etoposide is mainly metabolized in phase I by CYP3A4/5 and in phase II by GSTs and UGT1A1. Therefore, polymorphic variants of these enzymes appear to contribute to etoposide clinical response [16].

On the other hand, DNA repair enzymes are also important, both in sensitivity and resistance to etoposide in patients. Excision repair cross-complementary 1 (ERCC1) and/or ERCC1-XPF complex are key factors involved in the process of nucleotide excision repair induced by several drugs, including etoposide through p38 MAPK. This is associated to resistance to DNA damage-based chemotherapy [17,18].

Besides, platinum containing drugs, including cisplatin, are alkylating-like agents used in several types of cancer. Its pharmacological effect could be due to three different mechanisms of action: 1) induction of crosslinking of guanines in the DNA double helix, 2) fragmentation of DNA by alkylation of bases, and 3) induction of erroneous base pairing that conducts to mutations. Contrary to etoposide, the action of cisplatin is cell cycle-independent [19] and its metabolic fate has not been completely elucidated. On this regard, there is little evidence that suggests this drug undergoes enzymatic phase II biotransformation mainly by GSTs and so these enzymes could be responsible for the variability on cisplatin response [20]. Moreover, GSTs, particularly GSPP1 appear to be a protective factor for cisplatin ototoxicity. The role of GSTM1 and GSTT1 polymorphisms need to be evaluated [4,21]. Additionally, platinum adducts are recognized by the cellular DNA repair system and resistance to platinum chemotherapy is observed by activity of either the nucleotide excision repair (NER), mismatch repair (MMR) or homologous recombination (HR) pathways. Mutations in key enzymes of these pathways result in sensitivity to platinum drugs [22]. Cisplatin pharmacogenomics has been studied in several cancers, including TCa, where various SNPs in NER have been investigated. For example, SNPs in ERCC1 and ERCC1 3'-NTR were found to be associated with improved overall survival. Cisplatin sensitivity has been associated with low expression of ERCC1 [13].

Finally, bleomicineis an antibiotic with antitumoral activity that selectively inhibits DNA synthesis by producing crosslinking of the DNA strand. High concentrations of bleomycin stop RNA and protein synthesis. *In vivo* bleomycin inhibits B and T lymphocytes and macrophage proliferation as well as γ-interferon, TNF-α and interleukin-2. Bleomycin hydrolase (BLMH) inactivates bleomycin [23]. It has been shown that the A1450G polymorphic site in BLMH gene (I443V) has clinical implicances in patients. de Haas et al. [24] gave strong evidence for the importance of BLMH pharmacogenomic studies in the treatment of patients with TCa, showing how the large overall difference in treatment outcomes can be attributed to a single SNP in BLMH [7]. Therefore, it seems quite understandable that efficacy and safety of bleomycin treatment can be influenced by polymorphisms in BLHM gene.

Final Considerations

Pharmacogenomic research is particularly focused on SNPs with high allele frequency that results in an altered response to drugs. In this sense, it is logical to assume that the variability in clinical response to anticancer agents could be due to tumor and host genetic factors. Thus, many association studies among SNPs in genes encoding for drug transport, uptake, metabolism, detoxification and DNA repair proteins and drug response, have been performed. The current challenge for personalized therapy of cancer is to define genetic profiles that help the prediction of a personalized response to drugs and the progression of the illness [21,25-30]. The answers to these hypotheses can be obtained only through case-control and prospective studies with pharmacogenomic basis.

Therefore, considering the current knowledge regarding the metabolism and response to chemotherapeutic agents, and based on the importance of this area in clinical practice, our research group has investigated the molecular basis of variable clinical response to the chemotherapeutic treatment in TCa patients, as a model (Fondecyt Grant No. 1140434). Our preliminary results show some pharmagenes (BLMH, ERCC1, CYPs) as good biomarkers of prognosis (data not published). TCa patients are convenient research subjects, because testicular tumors allow the analysis of transformed cells by removing a routine sample with low injury to the patient. Moreover this is a cancer with good prognosis after surgical and pharmacological treatment, which allows us to know efficacy and safety of drugs with at least one-year follow-up. Thus, we encourage researchers to develop more studies on chemotherapy of testicular cancer and other tumors to support the usefulness of SNPs as biomarkers in order to improve pharmacotherapeutic response.

We strongly believe that the study of pharmacogenomics of TCa will help to define the potential clinical use of genetic polymorphisms in pharmagenes as biomarkers for cancer patients' response and inter-ethnic differences, not only for single polymorphisms but also the function of simultaneous polymorphisms in each patient exposed to chemotherapy [31]. Besides, the role of environmental factors as risk and prognosis modifier factors should be evaluated.

References

1. Adra N, Einhorn LH. Testicular cancer update. Clin Adv Hematol Oncol. 2017;15(5):386-96.

2. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. Guidelines on testicular cancer. London: European Association of Urology, UK; 2015.

3. Cancer Stat Facts: Testis Cancer. Bethesda: National Cancer Institute, NIH, USA.

4. Oldenburg J, Kraggerud SM, Brydøy M, Cvancarova M, Lothe RA, Fossa SD. Association between long-term neuro-toxicities in testicular cancer survivors and polymorphisms in glutathione-s-transferase-P1 and -M1, a retrospective cross sectional study. J Transl Med. 2007;5:70.

5. Travis LB, Beard C, Allan JM, Dahl AA, Feldman DR, Oldenburg J, et al.

Testicular cancer survivorship: research strategies and recommendations. J Natl Cancer Inst. 2010;102(15):1114-30.

6. Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA. 2008;299(6):672-84.
7. Bokemeyer C. Bleomycin in testicular cancer: will pharmacogenomics improve treatment regimens? J Clin Oncol. 2008;26(11):1783-5.
8. Ingelman-Sundberg M, Sim SC. Pharmacogenetic biomarkers as tools for improved drug therapy; emphasis on the cytochrome P450 system. Biochem Biophys Res Commun. 2010;396(1):90-4.
9. Quiñones LA, Rosero M, Roco A, Moreno I, Sasso J, Varela N. Role of cytochrome p450 enzymes in antineoplastic drug metabolism: Current status and therapeutic perspectives. Rev Med Chile. 2008;136(10):1327-35.
10. Kuptsova-Clarkson N, Ambrosone CB, Weiss J, Baer MR, Sucheston IE, Zirpoli G, et al. XPD DNA nucleotide excision repair gene polymorphisms associated with DNA repair deficiency predict better treatment outcomes in secondary acute myeloid leukemia. Int J Mol Epidemiol Genet. 2010;1(4):278-94.
11. Gossage L, Madhusudan S. Cancer pharmacogenomics: role of DNA repair genetic polymorphisms in individualizing cancer therapy. Mol Diagn Ther. 2007;11:361-80.
12. Giovannetti E, Pacetti P, Reni M, Leon LG, Mambrini A, Vasile E, et al. Association between DNA-repair polymorphisms and survival in pancreatic cancer patients treated with combination chemotherapy. Pharmacogenomics. 2011;12(12):1641-52.
13. Bradbury P, Kulke M, Heist R, Zhou W, Ma C, Xu W, et al. Cisplatin pharmacogenetics, DNA repair polymorphisms, and esophageal cancer outcomes. Pharmacogenet Genomics. 2009;19(8):613-25.
14. Russell LB, Hunsicker PR, Hack AM, Ashley T. Effect of the topoisomerase-II inhibitor etoposide on meiotic recombination in male mice. Mutat Res. 2000;464(2):201-12.
15. http://www.drugbank.ca/drugs/DB00773.
16. Yang J, Bogni A, Schuetz EG, Ratain M, Dolan ME, McLeod H, et al. Etoposide pathway. Pharmacogenet Genomics. 2009;19(7):552-3.
17. Mcneil EM, Melton DW. DNA repair endonuclease ERCC1-XPF as a novel therapeutic target to overcome chemoresistance in cancer therapy. Nucleic Acids Res. 2012;40(20):9990-10004.
18. Tsai MS, Weng SH, Chen HJ, Chiu YF, Huang YC, Tseng SC, et al. Inhibition of p38 MAPK-dependent excision repair cross-complementing 1 expression decreases the DNA repair capacity to sensitize lung cancer cells to etoposide. Mol Cancer Ther. 2012;11(3):561-71.
19. http://www.drugbank.ca/drugs/DB00515.
20. Petros W, Hopkins P, Spruill S, Broadwater G, Vredenburgh JJ, Colvin OM, et al. Association between drug metabolism genotype, chemotherapy pharmacokinetics, and overall survival in patients with breast cancer. J Clin Oncol. 2005;23(25):6117-25.
21. Roco A, Cayún J, Contreras S, Stojanova J, Quiñones L. Can pharmacogenetics explain efficacy and safety of cisplatin pharmacotherapy? Front Genet. 2014;5:391.
22. van der Straaten T, Mullenders L, Guchelaar HJ. Pharmacogenetics of Cancer and DNA Repair Enzymes. InTech. 2011.
23. https://www.drugbank.ca/drugs/DB00290.
24. de Haas EC, Zwart N, Meijer C, Nuver J, Boezen HM, Suurmeijer AJ, et al. Variation in bleomycin hydrolase gene is associated with reduced survival after chemotherapy for testicular germ cell cancer. J Clin Oncol. 2008;26:1817-23.
25. Gardiner SJ, Begg EJ. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. Pharmacol Rev. 2006;58(3):521-90.
26. Huang SM, Goodsaid F, Rahman A, Frueh F, Lesko LJ. Application of pharmacogenetics in clinical pharmacology. Toxicol Mech Methods. 2006;16(2-3):89-99.
27. Acevedo CA, Quiñones LA, Catalán J, Cáceres DD, Fullá JA, Roco AM. Impact of CYP1A1, GSTM1, and GSTT1 polymorphisms in overall and specific prostate cancer survival. Urol Oncol. 2014;32(3):280-90.
28. Mancinelli I, Cronin M, Sadee W. Pharmacogenomics: the promise of personalized medicine. AAPS Pharm Sci. 2000;2(1):E4.
29. Roco A, Quiñones L, Agúndez J, García-Martín E, Squicciarini V, Miranda C, et al. Allele frequencies of 23 functionally significant variant alleles related with metabolism of antineoplastic drugs in the Chilean population: comparison with Caucasian and Asian populations. Front Genet. 2012;3:229.
30. Quiñones L, Lee K. Improving cancer chemotherapy through pharmacogenomics. a research Topic. Front Genet. 2015;6:195.
31. López-Cortés A, Guerrero S, Redal MA, Alvarado AT, Quiñones LA. State of art of cancer pharmacogenomics in latinamerican populations. Int J Mol Sci. 2017;18(6).