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Review

Genetic Polymorphisms as Treatment Biomarkers for Gynecological Malignancies Treated With Carboplatin and Paclitaxel: A Systematic Review

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ABSTRACTS

Purpose

Gynecological tumors, which correspond to the group of neoplasms that affect the female reproductive system, have high incidence and mortality rates. This systematic review aimed to summarize the most recent advances in identifying pharmacogenetic variants associated with the clinical outcomes of carboplatin-paclitaxel chemotherapy in these patients.

Methods

A comprehensive literature search was conducted across eight databases to identify studies published up to July 17, 2024. Two reviewers independently selected the studies and extracted the data; disagreements were resolved by two additional reviewers.

Findings

Out of the 2375 records that were found, only 20 met the eligibility criteria. The main findings were: (1) The three most extensively investigated genes were ATP binding cassette subfamily C member 1 (*ABCB1*), cytochrome P450 2C8 (*CYP2C8*), and glutathione S-transferase P1 (*GSTP1*); (2) three variants, rs1128503 (*ABCB1*), rs10509681 and rs11572080 (*CYPC28*), appear to have a significant association with important adverse drug reactions (in particular, neutropenia, thrombocytopenia, and peripheral sensory neuropathy). Others, as is the case with rs1045642 (*ABCB1*) and rs1695 (*GSTP1*), have inconsistent results, and the extent to which these results can be extrapolated is still limited; and (c) most of the included studies concerned Asian or European patients.

Implications

Therefore, future research should include more extensive analyses with more inclusive cohorts. As a limitation of the study, a meta-analysis was not possible due to the significant heterogeneity among the studies.

Introduction

Gynecological cancers correspond to the group of neoplasms that affect the female reproductive system, encompassing tumors of the ovary, endometrium (corpus uteri), cervix, and vulva, and less frequently, tumors of the vagina and fallopian tube.[1] With a significant global impact on women's health, gynecological cancers were among the 15 most prevalent cancers for this group in 2022, both in terms of incidence and mortality.[2]

The higher mortality rates may be partly attributed to the challenging process of diagnosis. The symptoms, which may include

changes in bowel habits, abdominal distension, and associated pain, are common but nonspecific symptoms of these malignancies. Therefore, it is challenging to discern between chronic symptoms and the ones that could potentially indicate the development of a tumor.3, 4, 5 For these reasons, most patients are diagnosed with advanced or metastatic disease, for which surgery in isolation is not appropriate.

According to the International Federation of Gynecology and Obstetrics (FIGO), the most recommended treatment regimen for recurrent or advanced stages of these tumors consists of adjuvant chemotherapy with the association of a platinum derivative and a taxane.[1] As previous clinical studies have shown, the combination of paclitaxel with carboplatin is preferred to cisplatin, due to its higher safety profile, as carboplatin has fewer nonhematological adverse drug reactions (ADRs) than its precursor cisplatin.6, 7, 8 However, despite the positive therapeutic effectiveness,[9] these two agents have well-established ADRs profiles in clinical practice. While the carboplatin myelosuppressive effects lead to hematologic ADRs, paclitaxel is most associated with peripheral neuropathy, characterized by damage or loss of function of peripheral sensory nerves.[8.10]

Although several factors contribute to interindividual differences in the incidence and severity of ADRs, it is well-recognized that genetic variations are a significant component.[11.12] Among them, single-nucleotide variants (SNVs) can be highlighted as the most common genetic variations across the human genome. Therefore, genetic variants in genes implicated with the pharmacokinetics or pharmacodynamics of these chemotherapeutic agents could induce substantial alterations in the transcription of essential proteins for both biological processes.[13]

Chemotherapy-induced ADRs are known to significantly impair patients' quality of life and treatment success, resulting in dose delays, dose reductions, or discontinuation. Identifying the main SNVs associated with interindividual variations of ADRs may provide a better understanding of cancer treatment, being especially important in the context of personalized medicine in clinical practice. Therefore, this systematic review aimed to provide a comprehensive overview of pharmacogenetic variants associated with the clinical outcomes of carboplatin-paclitaxel chemotherapy in patients with gynecological tumors.

Section snippets

Materials and Methods

This review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) 2020 checklist and reporting guideline.[14] The review protocol was registered in Open Science Framework (https://doi.org/10.17605/OSF.IO/Q3SX7 ↗, last updated on May 08, 2024). …

Results

The initial search identified 3305 studies from multiple databases, with 930 overlapping references. From the remaining 2375 articles, 2202 were excluded after reviewing their titles and abstracts. The full text of the remaining 173 articles was thoroughly reviewed, and the main reasons for excluding 152 of them were: (1) The treatment protocol was not specified or did not include paclitaxel and carboplatin; (2) multiple diagnoses or treatments were included in the study without providing …

Discussion

This systematic review aimed to provide a detailed synthesis of the genetic polymorphisms associated with ADRs and treatment effectiveness of carboplatin-paclitaxel chemotherapy in patients with gynecological malignancies. Therefore, the systematic research identified 20 studies, of which 11 reported significant SNV-ADR associations, and 10 showed SNV significant associations with treatment effectiveness.

Interindividual variability in response and ADRs to the same treatment emphasizes the …

Conclusion

This systematic review included a total of 20 studies. The main strength of this review is the comprehensive overview and description of pharmacogenomic investigations to date. Three variants, rs1128503 (*ABCB1*), rs10509681, and rs11572080 (*CYPC28*), appear to have a significant association with important ADRs (in particular neutropenia, thrombocytopenia, and peripheral sensory neuropathy) in patients with gynecological tumors who undergo combined paclitaxel and carboplatin chemotherapy. Others, …

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Author contributions

Conceptualization, N.d.G.T., M.B.V., and P.M.; methodology, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., E.d.C.P., and P.M.; formal analysis, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., J.E.M., B., E.d.C.P., and P.M.; investigation, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., E.d.C.P., and P.M.; resources, E.d.C.P., P.C.J.L.S., and P.M.; data curation, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., E.d.C.P., and P.M.; writing—original draft preparation, N.d.G.T. and Y.G.M.; writing—review and …

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. …

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References (70)

D. Weinberg *et al.*
Vulvar cancer
Obstet Gynecol Clin North Am (2019)

R.L. Coleman *et al.*
Bevacizumab and paclitaxel–carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial
Lancet Oncol (2017)

H. Gréen *et al.*
ABCB1 G1199A polymorphism and ovarian cancer response to paclitaxel
J Pharm Sci (2008)

S.B. Park *et al.*
Clinical and genetic predictors of paclitaxel neurotoxicity based on patient- versus clinician reported incidence and severity of neurotoxicity in the ICON7 trial
Ann Oncol (2017)

K.D. Steffensen *et al.*
The relationship of VEGF polymorphisms with serum VEGF levels and progression-free survival in patients with epithelial ovarian cancer
Gynecol Oncol (2010)

L. Guo *et al.*
Genetic variations in the PI3K/AKT pathway predict platinum-based neoadjuvant chemotherapeutic sensitivity in squamous cervical cancer
Life Sci (2015)

H. Gréen *et al.*
Impact of CYP3A5*3 and CYP2C8-HapC on paclitaxel/carboplatin-induced myelosuppression in patients with ovarian cancer

J Pharm Sci (2011)

U.M. Zanger *et al.*

Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation

Pharmacol Ther (2013)

J.T. Backman *et al.*

Role of cytochrome P450 2C8 in drug metabolism and interactions

Pharmacol Rev (2016)

B. Achour *et al.*

Expression of hepatic drug-metabolizing cytochrome P450 enzymes and their intercorrelations: a meta-analysis

Drug Metab Dispos (2014)

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