

Case Report

A Rare Toxicity to Chemotherapy

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Abstract

The use of chemotherapy is often limited by toxic side-effects caused to healthy cells. In general, most chemotherapy treatments cause DNA damage or stop cells in mitosis, targeting both cancer and healthy cells. Life-threatening toxicities of chemotherapies can occur with varying frequency depending on the agent suspected and underlying patient risk factors. Post-chemotherapy fatal toxicity is comparatively rare. They occur mostly after high-dose chemotherapy. Pharmacogenomics is a potential and growing field of research that can help in the individualization of therapy based on responses and toxicity. We report a case of a young man with a carcinoma of the right upper alveolus. He was started on weekly chemoradiation with low-dose cisplatin. After the second cycle, he developed persistent pancytopenia, which never recovered after 3 weeks of admission in the hospital for supportive care. This case highlights the importance of pharmacogenomics in medical oncology. It can also help in counseling the patient and relatives, especially when there is a high degree of suspicion of an elevated amount of toxicities. There has been considerable research into pharmacogenomics in the past decade, and functional genomic approaches are likely to be used in future as an important resource for the prediction of clinical outcome.

Keywords: Cis platinum, low dose, pharmacogenomics, toxicity

INTRODUCTION

Chemotherapy is an important component of treatment for many cancers, and new anti-cancer drugs represent one of the largest areas of pharmaceutical development. However, the nature of chemotherapy means that while damaging cancer cells, it also damages healthy cells, leading to side effects. The side-effects and long-term sequelae of anti-cancer chemotherapy remain a major source of concern for both patients and clinicians despite the improved efficacy and enhanced survival offered by modern treatments. Chemotherapy-related toxicities commonly occur with high-dose chemotherapy. They are graded as per the Common Terminology Criteria for Adverse Event grading system into five categories.

Pharmacogenomics is one of the core elements in personalized medicine. The basic concept is that interindividual variability in drug response is a consequence of multiple factors, including genomics, epigenomics, the environment, and a patient's characteristics, such as gender, age, and/or concomitant medication.

Here, we are reporting a rare, fatal case of toxicity to a low-dose of chemotherapy in the young man. It highlights the importance of the field of pharmacogenomics in Medical Oncology.

CASE REPORT

A 31-year-old man with no comorbidities presented in February 2019 with swelling in the right upper alveolus for 2 months. The biopsy of the swelling revealed a squamous cell carcinoma. He underwent surgery with flap reconstruction on June 10, 2019. The resected specimen showed moderately differentiated squamous cell carcinoma with positive lymph nodes and extranodal extension. He was advised adjuvant chemoradiation.

He gave a family history of his brother expiring due to some malignancy after the first cycle of chemotherapy. The family did not have any further records of the deceased sibling.

He was started on radiotherapy with concurrent weekly cisplatin at 40 mg/m². The first cycle of cisplatin was uneventful.

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Postsecond cycle of cisplatin, he developed grade 3 diarrhea. He had pancytopenia. He developed febrile neutropenia. His blood culture revealed a growth of coagulase-negative *Staphylococcus aureus* and non-albicans candida. He was started on growth factor support with filgrastim and intravenous antibiotics and antifungals in a dose-escalated approach. He was supported with blood products in the form of fresh frozen plasma, packed cells, and platelets. His blood counts did not recover even after 3 weeks of admission. The hemophago lymphohistiocytosis workup which includes fibrinogen, lactate dehydrogenase, triglycerides, and ferritin was normal. The bone marrow aspiration and biopsy revealed an aplastic picture. We were planning to further investigate for the cause of pancytopenia, including genetic workup and chromosome fragility testing but he succumbed to neutropenic sepsis and fungal pneumonia.

DISCUSSION

To the best of our knowledge, this is the first case report of fatal toxicity to chemotherapy with low-dose *cis*-platinum. Chemotherapy-induced bone marrow suppression is the major dose-limiting toxicity of several chemotherapy drugs. It is associated with substantial morbidity, mortality, and costs. Hematological toxicity with chemotherapy is common with most of the chemotherapy drugs. High-dose chemotherapy, especially that given in hematological malignancy and transplant, is associated with prolonged pancytopenia.

Several genetic causes of chemotherapy-induced toxicity have been reported. Pharmacogenomics represents a promising future for the individualization of therapy. Several genetic polymorphisms and haplotypes have been investigated in an attempt to optimize therapy with specific drugs. However, their clinical applications are still controversial.^[1] Commonly used tests for predicting the likelihood of toxicity include dihydropyrimidine testing for 5-fluorouracil, thiopurine S-methyl transferase for thiopurines and UDP glucuronosyltransferase (UGT1A1) for irinotecan.

There are significant differences between cancer and other disease pharmacogenomics. In cancer, both germline genome of the patient and the somatic genome of the tumor are involved. The former is responsible for the inter-individual inherited genetic differences while the latter is due to the accumulation of acquired somatic mutations resulting in inconsistent responses.^[2]

As for the platinum compounds, pharmacogenomics in relation to response and toxicity is in the research phase and

testing is not routinely done. The key genes involved include *ERCC1*, *ERCC2 (XPD)*, *ERCC5*, *XRCC1*, *XRCC3*, and *XPC* genes. Studies examining the genetic variability of cisplatin metabolism have shown that the main genes involved are *GSTP1*, *GSTM3*, *GSTM1*, and *GSTT1*. Currently, there appears to be a group of genes that would influence variability in response and toxicity in cisplatin-based therapies.^[3]

In our case, with the presence of similar family history in the sibling of fatal chemotherapy-induced toxicity, pharmacogenomics study, and genetic testing was warranted. We hope to test the rest of the family for germ-line defects, increasing their susceptibility to cisplatin.

CONCLUSION

A patient's genetic composition strongly influences how chemotherapeutic agents are absorbed, distributed, metabolized, and excreted by the body. Consequently, variations in genes that are responsible for these activities play a significant role in determining the prognostic outcome for patients.^[4] Studying and identifying these associated genes have been the main foci of chemotherapy research, and much progress has been made in understanding the metabolic relationship between genes and chemotherapeutic agents. This understanding can be used to personalize chemotherapy regimens and ensure that treatment benefits outweigh treatment risks. Our case report reiterates the need for developing pharmacogenomics and its judicious use in the field of medical oncology.

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Conflicts of interest

There are no conflicts of interest.

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