Microreviews in Cell and Molecular Biology
An undergraduate science journal
2023

Side effects of chemotherapy and their management

Author: Emma Appel
Major: Pharmacy
Department of Microbiology and Molecular Genetics, Oklahoma State University, Stillwater, OK 74078, USA

Key Words:
Chemotherapy, acute side effects, long-term side effects, toxicities

Chemotherapy is the most common cancer treatment, often used in combination with other therapies, such as surgery, radiation, or hormone therapy. It relies on the use of drugs to destroy cancer cells and generally comes with a wide range of side effects such as anemia, neutropenia, nausea, vomiting, diarrhea, and mucositis. Chemotherapy induced side-effects occur in more than 50% of the patients. They are various and multifactorial, depending on the type of cancer, location, drugs, and dose. Acute and immediate side effects can be treated or managed and most will stop after the treatment ends. Antiemetic medicines and painkillers constitute a therapeutical solution. Nevertheless, some other side effects can persist due to permanent damages (on specific organs: heart, lungs, kidneys, etc). Furthermore, the extreme and sometimes long-lasting side effects of chemotherapeutic agents are cause for investigation into non-traditional therapies like integrative medicines.

Introduction

Cancerous cells acquire abnormal properties related to the cell cycle. Thus, they gain the ability to proliferate indefinitely (immortalization) with reduced requirement for mitogenic growth factors. Chemotherapy, relying on the use of pharmaceutical and chemical agents, mainly targets these characteristics, and often DNA, to treat cancers. As a result, there are various chemo drugs that can be classified into different categories, such as the alkylating agents (cisplatin, carboplatin), the antimetabolites (5-flourouracil, methotrexate), the topoisomerase inhibitors (etoposide, irinotecan), the mitotic spindle inhibitors/ plant alkaloids (paclitaxel, vincristine) and some other cytotoxic agents like antibiotics (doxorubicin, bleomycin).

Chemotherapy drugs all have distinct mechanisms of action acting on the cell cycle. Unfortunately, these treatments lack selectivity and will damage rapidly growing cells in both cancerous and normal populations. It leads to the principal side-effects of chemotherapy and the acute effects occurring during the treatment period. The bone marrow, gastrointestinal mucosa, hair follicles, and gonads are among the most sensitive tissues in the body regarding the destruction of rapidly dividing cells (Corrie, 2008). Thus, they are going to be involved in the common immediate side effects. Patients will experience myelosuppression, nausea, vomiting, hair loss, and effects on the reproductive systems.

Spermatogenesis and oogenesis are impacted, leading to reduced fertility. On the other hand, the majority of cytotoxics are teratogenic and potentially harmful to the foetus. Other common side effects are associated with most of the chemotherapy drugs like, tiredness, loss of appetite, muscle pain, or even headaches. However, the encountered side effects are highly variable, depending on multiple factors. The type of drug is one of the main factors with the age of the patients, the gender, the overall health status, and the type of cancer. Other elements shouldn't be neglected such as, the dose and the duration of the treatment. For instance, platinum-based chemotherapy drugs cisplatin, carboplatin, and oxaliplatin are limited by their severe, dose-limiting side effects (Oun et al., 2018). They all have dose-limiting toxicity, a side effect of a drug that is serious enough to prevent an increase in dose or level of that treatment. Therefore, for cisplatin, the dose-limiting toxicity is nephrotoxicity (mainly acute kidney injury and hypomagnesemia). Nephrotoxicity appears to be higher after two cycles of chemotherapy than after one (Faig et al., 2019). Cisplatin can damage other organs and tissues like the ears provoking ototoxicity. It causes hearing loss at high frequencies (>4 kHz) proportional to the dose or cumulative dose. Hearing loss is common when the cisplatin dose is greater than 60 mg/m2. Studies (Oun et al., 2018) also showed that patients receiving 20mg/m2 of cisplatin daily for five days were less impacted than those receiving 100mg/m2 in one day.

Long-term consequences and toxicities can also be present to the extent that cytotoxic drugs can cause permanent and specific damages. These effects are observed months or even years after the treatment and differ in severity. Thus, patients can present cardiotoxicity (arrhythmias, cardiac ischemia), nephrotoxicity, pulmonary toxicity (pneumonia), neurotoxicity (peripheral neuropathy) or even second cancer. High-risk groups for these late effects include young patients cured of Hodgkin's disease, acute leukaemia and testicular cancer (Pippa, 2008).

Recent Progress

Cancer therapy has improved over the past decade with the introduction of combination drug regimens, adjuvants, and targeted therapies. However, the spectrum of side effects has also expanded. Moreover, side effects do not only impact quality of life, but also treatment outcomes. Hence, prophylactic measures and an adequate management of these sides effects and long-term consequences are essential to improve the well-being of patients. The side effects being very diverse, the therapeutic arsenal to manage them is very broad too. Chemo protectants, defined as "natural or synthetic chemical compounds exhibiting the ability to ameliorate, mimic, or inhibit the toxic or adverse effects of structurally different chemotherapeutic agents" (Schwab, 2017) constitute an option for treatment. They are administered as cytoprotective adjuvants, providing site-specific protection for normal tissues without compromising antitumor efficacy. Several chemoprotectants are well-documented such as dexrazoxane, amifostine and glutathione. For example, dexrazoxane is used to prevent doxorubicin-induced cardiotoxicity (Osataphan et al., 2023). Nevertheless, these compounds are specific to the cytotoxic drugs utilized. The management of side effects is more centered on the immediate acute side effects as long-term consequences are complex to apprehend and treat (for example hepatotoxicity) (Nurgali et al., 2018). Thus, patients suffering from long-term side effects like neurotoxicity (peripheral neuropathy) can't be treated (Hu et al., 2019). On the other hand, cancer pain (neuropathic, somatic, and visceral) can be managed with a wide range of drugs depending on the severity (Scarboroug et al., 2018). For mild and moderate pain, non-opioids drugs are used like nonsteroidal anti-inflammatory drugs (aspirin, ibuprofen) and for example acetaminophen. For moderate to severe pain, opioids (oxycodone, hydrocodone, fentanyl) provide some relief. Gastrointestinal toxicities (nausea/ diahhrea/ constipation), very common during

chemotherapy, can be addressed via a combination of antiemetic medicines (Gupta et al., 2021) such as corticosteroids (dexamethasone), monoamine antagonists (olanzapine), serotonin antagonists (ondansetron) and NK1 antagonist drug (aprepitant). Antioxydant supplements (vitamin E, selenium) have reported reduced toxicities (hepatotoxicity). Multivitamin and mineral supplements are useful to maintain general health and improving outcome after diagnosis but also to avoid deficiency that could occur (Harvie, 2014). Other integrative and alternative therapies like traditional Chinese medicine, acupuncture or cannabis can also help patients deal with their side effects (Smith et al., 2014).

Discussion

Chemotherapy-induced side effects remain a major challenge in cancer treatment, and effective management strategies are needed. While various options are available, they are limited by the specificity of the cytotoxic drugs used. For instance, amifostine, a chemoprotectant is used to decrease the cumulative nephrotoxicity caused by cisplatin for ovarian or lung cancer. Pain killers are also commonly used to lessen cancer pain and pain caused by chemotherapy. However, these medicines present adverse effects like constipation, sedation, and neurologic effects. Therefore, the use of pain killers and more specifically opioids must be regulated and carefully controlled to achieve a balance between their beneficial and negative effects. To a lesser extent, nutritional and antioxidant supplements seem to have an impact on the reduction of side effects but still contribute to avoid deficiencies. Nevertheless, the efficiency of these supplements is still questioned. Antioxidants have variable effects on chemotherapy toxicity and may reduce its toxicity of chemotherapy. However, their effects can be variable, and some studies suggest that they may even increase the risk of certain types of cancer. For example, vitamins such as vitamin E increase risk of lung, stomach, prostate cancer, and colorectal cancers and overall mortality in the general population, questioning its utilization for supplements.

The future of chemotherapy lies in developing targeted therapies that selectively attack cancer cells while sparing healthy cells. This approach would minimize side effects and improve patients' quality of life. One promising avenue is the use of immunotherapy, which harnesses the power of the immune system to fight cancer. Another promising development is the use of nanoparticles to deliver drugs directly to cancer cells, minimizing damage to healthy cells.

References

Corrie, P. G. (2008). “Cytotoxic chemotherapy: Clinical aspects”. Medicine, 36(1), 24–28.

Oun, R., Moussa, Y. E., & Wheate, N. J. (2018).“The side effects of platinum-based chemotherapy drugs: a review for chemists”. Dalton Transactions,. 47(19), 6645–6653.

Faig, J., Haughton, M., Taylor, R. C., D'Agostino, R. B., Jr, Whelen, M. J., Porosnicu Rodriguez, K. A., Bonomi, M., Murea, M., & Porosnicu, M. (2018). “Retrospective Analysis of Cisplatin Nephrotoxicity in Patients With Head and Neck Cancer Receiving Outpatient Treatment With Concurrent High-dose Cisplatin and Radiotherapy”. American journal of clinical oncology, 41(5), 432–440.

Schwab, M. (2017) “Chemoprotectants”.Encyclopedia of Cancer, 778–785.

Osataphan, N., Leemasawat, K., Phrommintikul, A., Chattipakorn, S. C., & Chattipakorn, N. (2023). “Chemotherapy-Induced Cardiotoxicity in Cancer Treatment: Mechanisms and Its Prevention”. Handbook of Cancer and Immunology. 1-31

Nurgali, K., Jagoe, R. T., & Abalo, R. (2018). « Adverse Effects of Cancer Chemotherapy: Anything New to Improve Tolerance and Reduce Sequelae?”. Frontiers in pharmacology, 9, 245.

Hu LY, Mi WL, Wu GC, Wang YQ, Mao-Ying QL. (2019) “Prevention and Treatment for Chemotherapy-Induced Peripheral Neuropathy: Therapies Based on CIPN Mechanisms”. Curr Neuropharmacol.. 17(2):184-196.

Scarborough, B. M., & Smith, C. B. (2018). “Optimal pain management for patients with cancer in the modern era”. A cancer journal for clinicians, 68(3), 182–196.

Gupta, K., Walton, R., & Kataria, S. P. (2021). “Chemotherapy-Induced Nausea and Vomiting: Pathogenesis, Recommendations, and New Trends”. Cancer treatment and research communications, 26, 100278.

Harvie, M. (2014). “Nutritional Supplements and Cancer: Potential Benefits and Proven Harms”. American Society of Clinical Oncology Educational Book, 34, e478–e486.

