Review Article

Title: Safety profile and toxicity amelioration strategies of common adverse effects associated with anticancer medications

Abstract

More than half the cancer patients undergoing cancer chemotherapy develop adverse drug effects. Cancer chemotherapy agents have a lower risk-benefit ratio than other treatments. Anticancer medications kill cancerous as well as the normal rapidly dividing cells including bone marrow cells, gastrointestinal epithelium, hair follicles, etc. They mainly cause nausea and vomiting, mucositis, constipation, diarrhea, hematological toxicities, cardiac toxicity, alopecia, gonadal toxicity, pulmonary toxicity, neurotoxicity, nephrotoxicity, etc. The severity of the adverse effects may range from mild nausea to life-threatening neutropenia. Administering premedication and antidotes are very vital in these patients. Upon the occurrence of adverse effects, immediate steps should be taken to manage them. Though the adverse effects due to anticancer medications are not avoidable, careful monitoring of the patients and modulating the drug schedules/dosages can help in minimizing them. Healthcare professionals should also develop strategies to minimize the occupational hazards associated with these drugs.

Keywords: Adverse effects, Alopecia, Cancer chemotherapy, Hematological toxicity, teratogenicity, vomiting

Word count of abstract: 145

Main Text

Introduction

Cancer is considered to occur as result of a disturbance in control mechanisms that control cell proliferation and differentiation.[1] Radiotherapy and chemotherapy along with surgery are the major treatment modalities available for the treatment of cancer.[2, 3] An ideal anticancer medicine should eradicate cancer cells without harming normal tissues. But the existing medicines for cancer cause substantial toxicity and the use of these medicines includes a careful consideration of benefits against toxicity.[4] In general, chemotherapy not only targets cancer cells but also other rapidly dividing normal cells of the human body.[5, 6] The damage to the normal cells produce various adverse effects which are also known as chemotherapy-induced adverse drug reactions. In this article, the authors discuss the various toxicities caused by anticancer medications and provide various methods for prevention, early diagnosis and management of these toxicities.

1. Nausea and Vomiting

One of the most common chemotherapies induced adverse drug reactions are nausea and vomiting, and can be broadly categorized as acute, delayed, or anticipatory.[7, 8] [Table 1]. Majority of the patients experience these adverse effects after getting chemotherapy treatment. The severity of nausea and vomiting heavily depend on the type of chemotherapy regime and dosage of individual drugs. The response of each individual to a given chemotherapy schedule varies.[8] The usage of newer antiemetic agents has considerably reduced the incidence of nausea and vomiting though they have abortive to prevent these totally.[9] Anticipatory nausea and vomiting are experienced by around 10- 44% of patients who take chemotherapy.[10]

Pathophysiology

Different anticancer agents act at different sites and few of them act at more than one site.[11] These sites include the chemoreceptor trigger zone (CTZ), and the gastrointestinal tract. Vestibular and

cortical mechanisms, altered taste and smell sensations may also contribute. The commonest mechanism is through the activation of CTZ.[12] Nausea and vomiting occurring within the first 24 hours of administration of chemotherapy are defined as acute, whereas those occurring after 24 are defined as delayed.[13] Anticipatory vomiting is a conditioned response typically occurring before the administration of chemotherapy.[13, 14]

Table 1. Emetogenic status of anticancer drugs[15]

Emetogenic status	Examples
Highly emetogenic drugs (causes vomiting in 75% or more of the cases)	Cisplatin, Cyclophosphamide, Cytosine arabinoside, Dacarbazine, Doxorubicin, Ifosfamide, Methotrexate, Mitomycin, Carmustine
Moderately emetogenic drugs (Causes vomiting in 50%-75% of the cases)	Carboplatin, Etoposide, Daunorubicin, Gemcitabine, Mitoxantrone, Topotecan, Cisplatin (< 40 mg/m^2), Doxorubicin (<60 mg/m^2), Cyclophosphamide (<1g)
Mildly emetogenic drugs (Causes vomiting in 25%-50% of the cases)	Asparaginase, Bleomycin, Busulfan, Chlorambucil, Cladribine, Docetaxel, Fludarabine, Fluorouracil, Hydroxyurea, Paclitaxel, Vincristine, Thiotepa, Melphalan

Management of chemotherapy-induced nausea and vomiting

For this purpose, patients are classified into three levels, level I (patients receiving mildly emetogenic agent), level II (patients receiving moderately emetogenic agent or patients receiving a mildly emetogenic agent who has failed to respond to at least two of the level I drugs) and level III

patients (patients receiving highly emetogenic agent, patients receiving 2 or more moderately emetogenic agents, patients who have failed a level II regimen).[16-18] [Table 2]

Table 2. Management of chemotherapy-induced nausea and vomiting

Levels	Management
Level I	1. Prochlorperazine 10mg P.O. before chemotherapy followed by 10mg P.O. 4-6th hourly after chemotherapy. 2. Dexamethasone 4mg P.O. before chemotherapy 3. Lorazepam 1mg P.O. 6th hourly.
Level II	1. Dolasetron 100mg P.O. or IV. or Ondansetron 10mg IV or Granisetron 10mg/kg I.V. before chemotherapy 2. Dexamethasone 8mg P.O. or 10mg I.V. before chemotherapy 3. Prochlorperazine 10mg P.O. 4-6th hourly after chemotherapy. 4. Lorazepam 1mg P.O. 6th hourly.
Level III	1. Dolasetron 100mg IV or Ondansetron 32mg IV or Granisetron 10mg/kg I.V. before chemotherapy 2. Dexamethasone 10-20mg I.V. before chemotherapy 3. Lorazepam 1mg PO before chemotherapy followed by 6th hourly after emotherapy 4. Metoclopramide 40mg PO 6th hourly x 4 days 5. Dexamethasone 4mg PO 6th hourly followed by 4mg 12th hourly for 1 day after chemotherapy

Corticosteroids are valuable antiemetics in preventing delayed emesis. Studies have shown an advantage for metoclopramide combined with steroids.[11, 17, 19] Lorazepam, is known to have some antiemetic effects.[11]

Delayed emesis: Two randomized studies, one with ondansetron and another with granisetron, indicated the usefulness of the serotonin antagonists for delayed emesis in patients receiving chemotherapy of intermediary emetogenicity.[11, 20]

II. Gastrointestinal toxicity

Several chemotherapeutic drugs damage rapidly dividing cells of the gastrointestinal tract and cause mucositis and diarrhea.[21, 22]

1. Mucositis

Oral mucositis is a known complication associated with cancer medicines.[23] Cells in the mouth usually undergo renewal every 7 to 14 days. Antimetabolites, hydroxyurea and procarbazine hydrochloride are commonly associated with this effect.[24] Upon occurrence, patients experience epithelial hyperplasia, epithelial dysplasia and collagen and glandular degeneration.[25, 26] Poor nutritional status is known to worsen this condition further.[27]

Non-pharmacological interventions

Non-pharmacological intervention includes consulting dentist at least 2 weeks before starting chemotherapy, asking the dentist regarding brushing and flossing, use of soft toothbrush and gentle cleaning, brushing teeth and gums after every meal, avoiding irritating, acidic foods and juices, and spicy, salty, coarse foods.[28]

Prophylactic measures and treatment

Chlorhexidine mouth wash, saline rinses, sodium bicarbonate rinses, betadine mouth wash, and ice are considered beneficial in preventing mucositis. Xylocaine, magnesium-based antacids, diphenhydramine, nystatin, and sucralfate, allopurinol, vitamin E and beta-carotene are also found to be beneficial.[28-30]

2. Diarrhea

Chemotherapy-induced diarrhea leads to alteration of patients' therapy, dose reductions of patients, dose delays in patients and complete termination of treatment.[31, 32] Drugs which induce diarrhea include 5-Fluorouracil, methotrexate, cytosine arabinose, capecitabine, and irinotecan. It is hard to forecast which patient is inclined to developing diarrhea. Management of diarrhea includes adequate fluid intake, oral rehydration preparations in mild to moderate diarrhea and intravenous fluid administration in case of severe fluid loss. Diarrhea can be controlled by Diphenoxylate+ Scopolamine 1 or 2 tabs. 3 or 4 times a day or Loperamide 2 capsules followed by 1 capsule after every loose stool (up to 8 capsules per day can be taken). However, the stool should be investigated to rule out infective pathology especially during the nadir period (10-14 days after administration of chemotherapy). Infective diarrhea is managed with appropriate antibiotics or antimicrobials. For diarrhea caused due to irinotecan, atropine is given if diarrhea occurs within 24 hrs. of drug infusion. If diarrhea occurs after 24 hrs. it is managed by Loperamide 2mg once every 2hrs up to 12 hrs. after diarrhea subsides.[32, 33]

3. Constipation

Constipation is often an underestimated complication in patients with advanced cancer.[34] Constipation can be caused by Vinca alkaloids like Vincristine, Vinblastine, Vinorelbine and drugs used in supportive care such as narcotic analgesics and calcium-containing antacids. Vinca alkaloids cause constipation within 7 days from the day of administration.[32]

Management

Constipation can be managed by a diet high in bulk fiber, fresh fruits, vegetables, adequate fluid intake and laxatives such as Senna or bisacodyl. Senokot is given as 2 tablets twice daily until regular bowel functioning followed by 1tab per day. Bisacodyl is given as 1 to 2 tablets per day if Senna is ineffective. Lactulose 30 ml 2 to 3 times daily or Milk of magnesia 30ml at bedtime can be added. Other alternatives include Cisapride 10 to 20 mg 6^{th} hourly, magnesium citrate, bisacodyl suppository, and enema.[32]

III. Hematological toxicity

1. Toxicity to White Blood Cells (WBCs)

White blood cells (WBCs) are affected further promptly, due to their short life duration resulting in neutropenia. They recover 3-4 weeks after chemotherapy. An absolute neutrophil count <1500/cmm will increase the risk of infections.[35, 36] To upsurge the WBC count, Granulocyte Colony Stimulating Factor (G-CSF) and Granulocyte-macrophage colony-stimulating factor (GM-CSF) are used frequently. G-CSF is administered subcutaneously at a dose of 300 mcg if the patient weighs less than 75 kg and 480 mcg if the patient's weight is 75kg or more. It causes adverse effects such as nausea, fever, bone pain which can be managed symptomatically. GM-CSF is administered intravenously or subcutaneously at a dose of 250 mcg/m^2. It causes adverse

effects such as fever, flushing, rigors and bone pain.[37] Febrile neutropenia is managed with appropriate drugs according to the treatment guidelines.[38, 39]

Preventive measures for the reduction of infection's threat

Patients should be told when the neutrophil count is low. The patient should be aware of the signs and symptoms of infection and report to the physician if he/she has any of the symptoms. When the neutrophil count is low, the infection can be prevented by avoiding crowds and persons with a cold, flu, or other infections. Keeping the body clean by bathing each day and washing hands after using the bathroom are recommended. The hands should be washed thoroughly before eating.

2. Toxicity to Platelets

Platelets are also affected due to the administration of chemotherapy resulting in thrombocytopenia. The usual time for the occurrence of thrombocytopenia is 10 to 21 days after the administration of chemotherapy.[40] Thrombocytopenia is managed with platelet transfusion when indicated. The usual indications for platelet transfusion include any evidence of bleeding, platelet count less than 10,000/cmm, platelet count less than 20,000/cmm with fever.[40, 41]

3. Toxicity to Red Blood Cells (RBCs)

RBCs are also affected during chemotherapy. Anemia due to chemotherapy-induced myelosuppression typically happens 2 to 3 weeks subsequently the administration of chemotherapy. This toxicity can be managed by transfusion of blood and erythropoietin 40,000 units per week subcutaneously.[42, 43]

IV. Hair Loss

Body hair loss (alopecia) is common in chemotherapy and the degree of body hair loss in patients on any chemotherapeutic duration is both dependent on antineoplastic agents and dose. Long-term treatment may bring about loss of pubic, axillary, and facial hair in addition to scalp hair. [44-46] Alopecia due to cancer chemotherapy is not irreversible and re-growth of hair occurs 1- 2 months after treatment termination. Alterations in color and texture of hair may happen: hair shade may lighten or darken and often is curling as it regrows. Doxorubicin and cyclophosphamide are common anticancer drugs known to cause epilation. Alopecia may be expected with other single-agent antibiotics, alkylating agents, nitrosoureas, and especially their combinations.[47, 48] Temporary vasoconstriction can reduce blood circulation in the scalp and can be beneficial in preventing hair loss by reducing access of the anticancer medicines to the hair follicles.[49]

V. Cardiac Toxicity

Anthracyclines, taxanes, cyclophosphamide, ifosfamide, vinca alkaloids, 5-fluorouracil, mitomycin-c, cisplatin, trastuzumab (Herceptin) are known to cause cardiac toxicity. Cardiomyopathy caused by the anthracyclines has three clinical presentations: acute, subacute, and late. The acute toxicity presents as myopericarditis, pericardial effusion, and myocardial dysfunction, sometimes leading to cardiac failure and occasionally death, within a few days of administration of the drug. The subacute presentation has an insidious onset and appears up to 200 days after the administration of the last dose. The late presentation occurs 5 or more years after completion of therapy.[50-53] Incidence of late abnormalities depends upon the cumulative dose of anthracycline received.[54-56]

Methods for preventing cardiomyopathy

Monitoring cardiac status, modification of drug delivery and use of cardioprotective agents are considered beneficial. Cardiac evaluation before anthracyclines and more monitoring previously each alternate treatment course till an aggregate dose of 300 mg/m^2 and declining the peak dose of anthracycline are known to be beneficial.[56-58]

Cardioprotective agents such as vitamin E, ascorbic acid, N-acetyl-cysteine, coenzyme Q10 and amifostine may be useful in minimizing cardiotoxicity.[59] Cardiomyopathy caused by anthracyclines can be managed with inotropic support and afterload reduction, angiotensin-converting enzyme inhibitors and selective beta-receptor blockers, such as metoprolol and carvedilol.[60, 61]

VI. Neurotoxicity

Chemotherapy may have detrimental effects on either the central or peripheral nervous system. Drugs causing neurotoxicity include vinca alkaloids, cisplatin, oxaliplatin, cytosine arabinose, ifosfamide, 5-fluorouracil, methotrexate, paclitaxel, docetaxel, procarbazine, fludarabine, cladribine, pentostatin, etc.[61]

Vinca alkaloids are known as the first class of drugs cause neurotoxicity. For vincristine, neurotoxicity is the main dose-limiting toxicity. The common signs caused by vincristine contain depression of the deep tendon reflexes, paresthesias of the distal extremities, motor dysfunction manifested as lower extremity weakness, cranial nerve involvement causing ophthalmoplegia and facial palsy, autonomic neuropathy causing orthostatic hypotension and erection/ejaculatory dysfunction.[62-64] Cisplatin and oxaliplatin-induced neuropathy can be manifested as sensory peripheral neuropathy, Lhermitte's sign, autonomic neuropathy, grand mal or focal seizures, encephalopathy, transient cortical blindness, retrobulbar neuritis, and retinal injury.[65]

Manifestations of cytosine arabinose induced neuropathy include cerebellar dysfunction, seizures, generalized encephalopathy, peripheral neuropathy, necrotizing leukoencephalopathy, spinal myelopathy, basal ganglia necrosis, and pseudobulbar palsy.[66] Neurotoxicity from methotrexate can manifest as meningeal irritation, transient paraparesis, or encephalopathy. When the drug is administered intrathecally (IT), it can cause headaches, nausea and vomiting, lethargy, nuchal rigidity, and other features of meningeal irritation.[67, 68]

Management

The mainstay of treatment involves the cessation of therapy and waiting for neurologic recovery. After cessation of therapy, neuropathy symptoms may continue for to 3 to 4 years. Vitamin therapy may not be very effective. Intestinal dysfunction from autonomic neuropathy may be improved by metoclopramide therapy. Neurotoxic symptoms may last for months after cisplatin therapy is discontinued. Recovery from the neurologic effects usually occurs within a few days after discontinuing cytarabine therapy.[69]

VII. Nephrotoxicity: Cisplatin, cyclophosphamide, ifosfamide, methotrexate, mitomycin, carmustine, lomustine and streptozocin are known to cause renal toxicity.[70] The pathologic lesion of cisplatin nephrotoxicity is seen primarily in the proximal and distal tubules but also may involve the collecting ducts, whereas the glomeruli are unaffected. The hemolytic uremic syndrome has been reported in patients treated with cisplatin.[70, 71]

Management

Higher doses of cisplatin require aggressive hydration. Mannitol also is used to enhance diuresis, Amifostine demonstrated significant protection against cisplatin-induced nephrotoxicity.[72, 73] Twenty-four-hour creatinine clearance value less than 70 mL/min, particularly in 60 years old or

more than 60 years old patients, is considered a contraindication for cisplatin therapy. [74] Treatment for mitomycin induced nephrotoxicity includes hemodialysis and plasmapheresis.[75] Methotrexate-induced renal insufficiency can be largely prevented by hydration and urine alkalization. Sequential hemodialysis and charcoal hemofiltration have been used as a treatment of acute nephrotoxicity from methotrexate.[71]

VIII. Hepatotoxicity: Several antitumor agents cause hepatic toxicity. The hepatotoxicity caused by chemotherapeutic drugs is manifested in three forms, which are chemical hepatitis, venoocclusive disease and chronic fibrosis. The antitumor drugs known to produce hepatotoxicity include l-asparaginase, carmustine, cytarabine, dactinomycin, etoposide, levamisole in combination with 5-fluorouracil, 6-mercaptopurine, and methotrexate in high doses, streptozocin, vincristine, busulfan and cyclophosphamide.[76, 77]

IX. Hypersensitivity reactions: Most of the antitumor agents can produce hypersensitivity reactions especially taxanes, which cause hypersensitivity reactions severe enough to stop the treatment. Paclitaxel and Docetaxel produce hypersensitivity reactions including bronchospasm, angioedema, hypotension and pneumonitis.[78] Antianaphylaxis medication must be readily available and the patient should be observed after the drug is administered to avoid these reactions. Paclitaxel and docetaxel are administered over a period of 1 to 3 hrs along with premedication using corticosteroids.[78, 79]

X. Gonadal dysfunction and teratogenicity: Infertility is an important problem for young adults treated with chemotherapy drugs.[80] In males, chemotherapy drugs result in loss of germinal cells leading to germinal aplasia. During the first 2 to 3 months of cytotoxic therapy, sperm counts may

remain normal or be only moderately reduced. Some regimens cause azoospermia.[81, 82] When sperm count recovers after cytotoxic therapy, fertility is generally restored. Drugs causing azoospermia include cisplatin, chlorambucil, cyclophosphamide, carmustine, and lomustine. [83-85] Methods to preserve fertility include semen cryopreservation, which is extremely important for men who want to preserve their fertility after cytotoxic treatment, and restoration of spermatogenesis is also possible with cryopreserved cells.[86, 87] In vitro fertilization (IVF), with artificial insemination, is important in achieving pregnancies from stored semen after the completion of cytotoxic therapy.[88] Ovulation may be temporarily stimulated by gonadotropin treatment and steroid hormone replacement therapy.[89]

XI. Cutaneous effects

Mucocutaneous surfaces are particularly susceptible to the lethal belongings of this category of anti-neoplastic agents, as these are composed of rapidly dividing cells.[90]

1. Nail complications: Nail involvement is dose-dependent, and may range from mild formation of multiple Beau's lines to severe onychomadesis, onycholysis and onychodystrophy. The big toe is the commonest nail to be affected. Nail pigmentation may be either diffuse or limited to the lunula or horizontal or vertical bands of pigmentation may occur. Anthracyclines (doxorubicin, daunorubicin) and taxanes (paclitaxel, docetaxel) commonly produce severe nail dystrophy and pigmentation in up to 40% of cases.[91]

2. Sweat gland abnormalities: Neutrophilic hidradenitis is a response form to a range of anti-neoplastic agents, the commonest being cytarabine and bleomycin. Clinically erythematous papules, plaques and nodules are seen, mainly on acral areas. Syringosquamous metaplasia is closely related

to neutrophilic hidradenitis and is due to the direct toxicity on sweat ducts by antineoplastic agents. Erythematous weals are seen, which resolve weeks after cessation of therapy. [92, 93]

3. Epidermal complications: The epidermal complications include toxic erythema and acral erythema.

a. Chemotherapy-induced toxic erythema: This is usually caused by busulfan, cytarabine, etoposide and methotrexate. There is a prodrome of tingling pain, followed by tender erythema and edema. Severe cases may resemble toxic epidermal necrolysis.[94, 95]

b. Chemotherapy-induced acral erythema: This is due to the concentration of drugs in sweat glands of palms and soles. Most common with cytarabine and doxorubicin. It develops in 1-3 weeks as sharply demarcated erythema of palms and soles.[96-98]

4. Keratoses: Multiple actinic and seborrhoeic keratoses may occur especially with fluorouracil and cytarabine.[99]

5. Hyperpigmentation: Bleomycin causes peculiar flagellate hyperpigmentation in 8-66% of cases.[100] Serpentine supravenous hyperpigmentation is caused by IV drugs like fluorouracil and vinorelbine. Daunorubicin causes polycyclic bands of scalp hyperpigmentation. Generalized hyperpigmentation is a common adverse effect of many cytotoxic agents, increased drug deposits due to increased blood flow, increase in melanocyte-stimulating hormone (MSH) secretion and drug-induced depletion of tyrosinase inhibitors.[101, 102]

7. Photosensitivity: Phototoxic reactions simulating sunburns are common. Photoallergic reactions are seen as papulovesicular, mainly seen over photo exposed areas. Radiation enhancement reaction is a synergistic reaction between antineoplastic drugs (Vinca alkaloids) and radiation.[103]

8. Dermal adverse effects: These include local injury due to extravasation leading to chemical cellulitis manifesting as erythema, induration and pain at IV infusion sites, or even ulcers and severe necrosis attributable to drugs like doxorubicin. Cisplatin and Asparaginase are well known to cause urticaria and angioedema (65% incidence). Sclerotic dermal reactions mimicking morphea are well known with bleomycin, docetaxel and melphalan. Raynaud's phenomenon may occur secondary to bleomycin and cisplatin.[104]

XII. Carcinogenic effects:

Busulfan may also be leukemogenic.[105] Several cases of acute leukemia have been reported in patients who developed pancytopenia 5 to 8 years earlier secondary to the use of busulfan. In an evaluation of 439 children with acute lymphoblastic leukemia (ALL), an increased risk for the development of secondary myelodysplasia (MDS) or acute myeloid leukemia (AML) was demonstrated when mercaptopurine was administered in patients with low thiopurine methyltransferase (TPMT) activity or excessively high intracellular levels of thioguanine nucleotides and methylated mercaptopurine metabolites.[106-108]

XIII. Miscellaneous adverse effects: Some of the other adverse effects due to anticancer drugs are mentioned below.

1. Tumor lysis syndrome: This syndrome occurs from the rapid destruction of chemotherapy-sensitive cells resulting in the release of intracellular phosphate, urates, and other cell contents. Burkitt's and similar fast-growing lymphomas, and less frequently in small cell lung cancer, breast cancer, and seminoma may show the syndrome.[109, 110] Administration of IV fluids, allopurinol and calcium gluconate are the usual methods of management.

2. Sepsis: In cancer patients undergoing combination chemotherapy, sepsis is a life-threatening condition.[111] A high incidence of streptococcal septicemia has been reported in patients with acute myelogenous leukemia following high-dose cytarabine therapy for remission induction or post remission intensive consolidation. Prophylactic regimens, including cotrimoxazole, were ineffective in preventing this complication. More studies are required to confirm these findings. [112, 113]

3. Injection site extravasation:

Leakage of vincristine into adjacent tissue throughout intravenous administration may cause significant irritation; avoid extravasation. Dactinomycin is very corrosive, and extravasation for the duration of IV administration can result in cellulitis and injury to soft tissues and contracture of the arms.[114, 115] It can be managed by stopping the infusion, injecting hydrocortisone around the site and use of icepack. It can be minimized by administering the drugs using central lines.[115]

Conclusion

The prevalence of cancer is increasing. Chemotherapy is an important treatment modality. A thorough investigation of the health status of the patient should be done before starting chemotherapy. Appropriate premedication and antidotes can be of great help in many conditions in minimizing the toxicity. On the occurrence of toxicity, immediate measures should be taken to

manage them. Though the toxicity profile of anticancer medications is unfavorable and some of the toxicities are not preventable, initiating appropriate steps can minimize these toxicities to a great extent. Apart from the adverse effects caused to the patients, these drugs can also cause serious hazards to the healthcare professions getting exposed to them. Hence all the healthcare professionals should take adequate preventive measures to minimize the exposure to the cancer chemotherapeutic agents as far as possible.

References

1. Cooper, G.M. and R.E. Hausman, *The development and causes of cancer.* The cell: A molecular approach, 2000: p. 725-766.
2. Arruebo, M., et al., *Assessment of the evolution of cancer treatment therapies.* Cancers, 2011. **3**(3): p. 3279-3330.
3. Baskar, R., et al., *Cancer and radiation therapy: current advances and future directions.* International journal of medical sciences, 2012. **9**(3): p. 193-199.
4. Lind, M.J., *Principles of systemic anticancer therapy.* Medicine, 2020.
5. Sak, K., *Chemotherapy and dietary phytochemical agents.* Chemotherapy research and practice, 2012. **2012**: p. 282570-282570.
6. Chakraborty, S. and T. Rahman, *The difficulties in cancer treatment.* Ecancermedicalscience, 2012. **6**: p. ed16-ed16.
7. Mustian, K.M., et al., *Chemotherapy-Induced Nausea and Vomiting.* US oncology, 2008. **4**(1): p. 19-23.
8. Schnell, F.M., *Chemotherapy-induced nausea and vomiting: the importance of acute antiemetic control.* Oncologist, 2003. **8**(2): p. 187-98.
9. Shaikh, S.I., et al., *Postoperative nausea and vomiting: A simple yet complex problem.* Anesthesia, essays and researches, 2016. **10**(3): p. 388-396.
10. Roscoe, J.A., et al., *Anticipatory nausea and vomiting.* Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2011. **19**(10): p. 1533-1538.
11. Berger, A.M., J.L. Shuster, and J.H. Von Roenn, *Principles and practice of palliative care and supportive oncology*. 2007: Lippincott Williams & Wilkins.
12. Borison, H., *Anatomy and physiology of the chemoreceptor trigger zone and area postrema*, in *Nausea and vomiting: Mechanisms and treatment*. 1986, Springer. p. 10-17.
13. Rapoport, B.L., *Delayed Chemotherapy-Induced Nausea and Vomiting: Pathogenesis, Incidence, and Current Management.* Frontiers in pharmacology, 2017. **8**: p. 19-19.
14. Kamen, C., et al., *Anticipatory nausea and vomiting due to chemotherapy.* European journal of pharmacology, 2014. **722**: p. 172-179.
15. Aoki, S., et al., *Difference in the emetic control among highly emetogenic chemotherapy regimens: Implementation for appropriate use of aprepitant.* Molecular and clinical oncology, 2013. **1**(1): p. 41-46.

16. Chan, V.T. and W. Yeo, *Antiemetic therapy options for chemotherapy-induced nausea and vomiting in breast cancer patients.* Breast cancer (Dove Medical Press), 2011. **3**: p. 151-160.
17. Rao, K.V. and A. Faso, *Chemotherapy-induced nausea and vomiting: optimizing prevention and management.* American health & drug benefits, 2012. **5**(4): p. 232.
18. Rashad, N. and O. Abdel-Rahman, *Differential clinical pharmacology of rolapitant in delayed chemotherapy-induced nausea and vomiting (CINV).* Drug Des Devel Ther, 2017. **11**: p. 947-954.
19. Gyawali, B., B.S. Poudyal, and M. Iddawela, *Cheaper options in the prevention of chemotherapy-induced nausea and vomiting.* Journal of global oncology, 2016. **2**(3): p. 145-153.
20. Griffin, C.E., et al., *Benzodiazepine pharmacology and central nervous system–mediated effects.* Ochsner Journal, 2013. **13**(2): p. 214-223.
21. Boussios, S., et al., *Systemic treatment-induced gastrointestinal toxicity: incidence, clinical presentation and management.* Annals of gastroenterology, 2012. **25**(2): p. 106-118.
22. Aprile, G., et al., *Treatment-related gastrointestinal toxicities and advanced colorectal or pancreatic cancer: A critical update.* World journal of gastroenterology, 2015. **21**(41): p. 11793-11803.
23. Plevová, P., *Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review.* Oral Oncol, 1999. **35**(5): p. 453-70.
24. Saadeh, C.E., *Chemotherapy- and Radiotherapy-Induced Oral Mucositis: Review of Preventive Strategies and Treatment.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2005. **25**(4): p. 540-554.
25. Shirani, S., et al., *Epithelial dysplasia in oral cavity.* Iranian journal of medical sciences, 2014. **39**(5): p. 406-417.
26. Ranganathan, K. and L. Kavitha, *Oral epithelial dysplasia: Classifications and clinical relevance in risk assessment of oral potentially malignant disorders.* Journal of oral and maxillofacial pathology : JOMFP, 2019. **23**(1): p. 19-27.
27. Ps, S.K., et al., *Radiation induced oral mucositis.* Indian journal of palliative care, 2009. **15**(2): p. 95-102.
28. Devi, S. and N. Singh, *Dental care during and after radiotherapy in head and neck cancer.* National journal of maxillofacial surgery, 2014. **5**(2): p. 117-125.
29. Mehdipour, M., et al., *A comparison between zinc sulfate and chlorhexidine gluconate mouthwashes in the prevention of chemotherapy-induced oral mucositis.* Daru : journal of Faculty of Pharmacy, Tehran University of Medical Sciences, 2011. **19**(1): p. 71-73.
30. Köstler, W.J., et al., *Oral Mucositis Complicating Chemotherapy and/or Radiotherapy: Options for Prevention and Treatment.* CA: A Cancer Journal for Clinicians, 2001. **51**(5): p. 290-315.
31. Stein, A., W. Voigt, and K. Jordan, *Chemotherapy-induced diarrhea: pathophysiology, frequency and guideline-based management.* Therapeutic advances in medical oncology, 2010. **2**(1): p. 51-63.
32. McQuade, R.M., et al., *Chemotherapy-Induced Constipation and Diarrhea: Pathophysiology, Current and Emerging Treatments.* Frontiers in pharmacology, 2016. **7**: p. 414-414.
33. Anigilaje, E.A., *Management of Diarrhoeal Dehydration in Childhood: A Review for Clinicians in Developing Countries.* Frontiers in pediatrics, 2018. **6**: p. 28-28.

34. Mancini, I. and E. Bruera, *Constipation in advanced cancer patients.* Supportive care in cancer, 1998. **6**(4): p. 356-364.
35. Lustberg, M.B., *Management of neutropenia in cancer patients.* Clinical advances in hematology & oncology : H&O, 2012. **10**(12): p. 825-826.
36. Newburger, P.E. and D.C. Dale, *Evaluation and management of patients with isolated neutropenia.* Seminars in hematology, 2013. **50**(3): p. 198-206.
37. Moore, D.C., *Drug-Induced Neutropenia: A Focus on Rituximab-Induced Late-Onset Neutropenia.* P & T : a peer-reviewed journal for formulary management, 2016. **41**(12): p. 765-768.
38. Lucas, A.J., J.L. Olin, and M.D. Coleman, *Management and Preventive Measures for Febrile Neutropenia.* P & T : a peer-reviewed journal for formulary management, 2018. **43**(4): p. 228-232.
39. Lyman, G.H. and K.V.I. Rolston, *How we treat febrile neutropenia in patients receiving cancer chemotherapy.* Journal of oncology practice, 2010. **6**(3): p. 149-152.
40. Slichter, S.J., et al., *Factors affecting posttransfusion platelet increments, platelet refractoriness, and platelet transfusion intervals in thrombocytopenic patients.* Blood, 2005. **105**(10): p. 4106-4114.
41. Izak, M. and J.B. Bussel, *Management of thrombocytopenia.* F1000prime reports, 2014. **6**: p. 45-45.
42. Bryer, E. and D. Henry, *Chemotherapy-induced anemia: etiology, pathophysiology, and implications for contemporary practice.* International Journal of Clinical Transfusion Medicine, 2018. **6**: p. 21.
43. Shrestha, S., et al., *Adverse drug reaction due to cancer chemotherapy and its financial burden in different hospitals of Nepal.* 2017.
44. Balagula, Y., S.T. Rosen, and M.E. Lacouture, *The emergence of supportive oncodermatology: the study of dermatologic adverse events to cancer therapies.* J Am Acad Dermatol, 2011. **65**(3): p. 624-635.
45. Olsen, E.A., *Chemotherapy-induced alopecia: overview and methodology for characterizing hair changes and regrowth*, in *The MASCC Textbook of Cancer Supportive Care and Survivorship*. 2010, Springer. p. 381-386.
46. Groopman, J.E. and L.M. Itri, *Chemotherapy-induced anemia in adults: incidence and treatment.* J Natl Cancer Inst, 1999. **91**(19): p. 1616-34.
47. Haslam, I.S. and E. Smart, *Chemotherapy-Induced Hair Loss: The Use of Biomarkers for Predicting Alopecic Severity and Treatment Efficacy.* Biomarker insights, 2019. **14**: p. 1177271919842180-1177271919842180.
48. Trüeb, R.M., *The difficult hair loss patient: A particular challenge.* International journal of trichology, 2013. **5**(3): p. 110.
49. Grevelman, E.G. and W.P. Breed, *Prevention of chemotherapy-induced hair loss by scalp cooling.* Ann Oncol, 2005. **16**(3): p. 352-8.
50. Floyd, J.D., et al., *Cardiotoxicity of Cancer Therapy.* Journal of Clinical Oncology, 2005. **23**(30): p. 7685-7696.
51. Gianni, L., E. Salvatorelli, and G. Minotti, *Anthracycline cardiotoxicity in breast cancer patients: synergism with trastuzumab and taxanes.* Cardiovasc Toxicol, 2007. **7**(2): p. 67-71.
52. Madeddu, C., et al., *Pathophysiology of cardiotoxicity induced by nonanthracycline chemotherapy.* J Cardiovasc Med (Hagerstown), 2016. **17 Suppl 1 Special issue on Cardiotoxicity from Antiblastic Drugs and Cardioprotection**: p. e12-e18.

53. Menna, P., E. Salvatorelli, and G. Minotti, *Cardiotoxicity of Antitumor Drugs.* Chemical Research in Toxicology, 2008. **21**(5): p. 978-989.
54. Sadurska, E., *Current Views on Anthracycline Cardiotoxicity in Childhood Cancer Survivors.* Pediatric cardiology, 2015. **36**(6): p. 1112-1119.
55. Volkova, M. and R. Russell, *Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment.* Current cardiology reviews, 2011. **7**(4): p. 214-220.
56. Bansal, N., et al., *Strategies to prevent anthracycline-induced cardiotoxicity in cancer survivors.* Cardio-Oncology, 2019. **5**(1): p. 18.
57. Rahman, A.M., S.W. Yusuf, and M.S. Ewer, *Anthracycline-induced cardiotoxicity and the cardiac-sparing effect of liposomal formulation.* International journal of nanomedicine, 2007. **2**(4): p. 567-583.
58. McGowan, J.V., et al., *Anthracycline Chemotherapy and Cardiotoxicity.* Cardiovascular drugs and therapy, 2017. **31**(1): p. 63-75.
59. Akbay, E., et al., *Effects of N-acetyl cysteine, vitamin E and vitamin C on liver glutathione levels following amiodarone treatment in rats.* Kardiochirurgia i torakochirurgia polska = Polish journal of cardio-thoracic surgery, 2019. **16**(2): p. 88-92.
60. Di Filippo, S., *Beta-adrenergic receptor antagonists and chronic heart failure in children.* Therapeutics and clinical risk management, 2007. **3**(5): p. 847-854.
61. Wu, A.H., *Management of patients with non-ischaemic cardiomyopathy.* Heart (British Cardiac Society), 2007. **93**(3): p. 403-408.
62. Loghin, M.E. and A. Kleiman, *Medication-Induced Neurotoxicity in Critically Ill Cancer Patients*, in *Oncologic Critical Care*, J.L. Nates and K.J. Price, Editors. 2020, Springer International Publishing: Cham. p. 319-334.
63. Mora, E., et al., *Vincristine-induced peripheral neuropathy in pediatric cancer patients.* American journal of cancer research, 2016. **6**(11): p. 2416-2430.
64. Starobova, H. and I. Vetter, *Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy.* Frontiers in molecular neuroscience, 2017. **10**: p. 174-174.
65. Staff, N.P., et al., *Chemotherapy-induced peripheral neuropathy: A current review.* Annals of neurology, 2017. **81**(6): p. 772-781.
66. Inaba, M., et al., *[Peripheral neuropathy, myelopathy, cerebellar ataxia, and subclinical optic neuropathy associated with copper deficiency occurring 23 years after total gastrectomy].* Rinsho Shinkeigaku, 2011. **51**(6): p. 412-6.
67. Cruz-Carreras, M.T., et al., *Methotrexate-induced leukoencephalopathy presenting as stroke in the emergency department.* Clinical case reports, 2017. **5**(10): p. 1644-1648.
68. Bhojwani, D., et al., *Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2014. **32**(9): p. 949-959.
69. de Caestecker, J.S., et al., *Evaluation of oral cisapride and metoclopramide in diabetic autonomic neuropathy: an eight-week double-blind crossover study.* Aliment Pharmacol Ther, 1989. **3**(1): p. 69-81.
70. Jia, J.B., et al., *Chemotherapy-related complications in the kidneys and collecting system: an imaging perspective.* Insights into imaging, 2015. **6**(4): p. 479-487.
71. Sharbaf, F.G., H. Farhangi, and F. Assadi, *Prevention of Chemotherapy-Induced Nephrotoxicity in Children with Cancer.* Int J Prev Med, 2017. **8**: p. 76.
72. Miller, R.P., et al., *Mechanisms of Cisplatin nephrotoxicity.* Toxins, 2010. **2**(11): p. 2490-2518.

73. Volarevic, V., et al., *Molecular mechanisms of cisplatin-induced nephrotoxicity: a balance on the knife edge between renoprotection and tumor toxicity.* Journal of Biomedical Science, 2019. **26**(1): p. 25.
74. Ahn, M.-J., et al., *Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: a literature review.* Oral oncology, 2016. **53**: p. 10-16.
75. Horie, S., et al., *Guidelines for treatment of renal injury during cancer chemotherapy 2016.* Clinical and experimental nephrology, 2018. **22**(1): p. 210-244.
76. Sharma, A., et al., *Chemotherapy induced liver abnormalities: an imaging perspective.* Clin Mol Hepatol, 2014. **20**(3): p. 317-326.
77. King, P.D. and M.C. Perry, *Hepatotoxicity of chemotherapy.* The oncologist, 2001. **6**(2): p. 162-176.
78. Boulanger, J., et al., *Management of hypersensitivity to platinum- and taxane-based chemotherapy: cepo review and clinical recommendations.* Current oncology (Toronto, Ont.), 2014. **21**(4): p. e630-e641.
79. Berger, M.J., et al., *Stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction.* Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 2015. **23**(7): p. 2019-2024.
80. Benedict, C., B. Thom, and J.F. Kelvin, *Fertility preservation and cancer: challenges for adolescent and young adult patients.* Current opinion in supportive and palliative care, 2016. **10**(1): p. 87-94.
81. Meistrich, M.L., *Effects of chemotherapy and radiotherapy on spermatogenesis in humans.* Fertility and sterility, 2013. **100**(5): p. 1180-1186.
82. Wallach, E.E., M.D. Damewood, and L.B. Grochow, *Prospects for fertility after chemotherapy or radiation for neoplastic disease.* Fertility and sterility, 1986. **45**(4): p. 443-459.
83. Meistrich, M.L., *Male gonadal toxicity.* Pediatric blood & cancer, 2009. **53**(2): p. 261-266.
84. Okada, K. and M. Fujisawa, *Recovery of Spermatogenesis Following Cancer Treatment with Cytotoxic Chemotherapy and Radiotherapy.* The world journal of men's health, 2019. **37**(2): p. 166-174.
85. Chiba, K. and M. Fujisawa, *Fertility preservation in men with cancer.* Reproductive Medicine and Biology, 2014. **13**(4): p. 177-184.
86. Wyns, C., *Male fertility preservation before gonadotoxic therapies.* Facts, views & vision in ObGyn, 2010. **2**(2): p. 88-108.
87. Hussein, A.A., N.D. Tran, and J.F. Smith, *Fertility preservation for boys and adolescents facing sterilizing medical therapy.* Translational andrology and urology, 2014. **3**(4): p. 382-390.
88. Zhang, A., et al., *Pregnancy and offspring outcomes after artificial insemination with donor sperm: A retrospective analysis of 1805 treatment cycles performed in Northwest China.* Medicine, 2019. **98**(16): p. e14975-e14975.
89. Sullivan, S.D., P.M. Sarrel, and L.M. Nelson, *Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause.* Fertility and sterility, 2016. **106**(7): p. 1588-1599.
90. Biswal, S.G. and R.D. Mehta, *Cutaneous Adverse Reactions of Chemotherapy in Cancer Patients: A Clinicoepidemiological Study.* Indian journal of dermatology, 2018. **63**(1): p. 41-46.

91. Singal, A. and K. Bisherwal, *Disorders of nail in infants and children.* Indian Journal of Paediatric Dermatology, 2019. **20**(2): p. 101.
92. Beutner, K.R., C.H. Packman, and W. Markowitch, *Neutrophilic eccrine hidradenitis associated with Hodgkin's disease and chemotherapy. A case report.* Arch Dermatol, 1986. **122**(7): p. 809-11.
93. Brehler, R., et al., *Neutrophilic hidradenitis induced by chemotherapy involves eccrine and apocrine glands.* Am J Dermatopathol, 1997. **19**(1): p. 73-8.
94. Yang, C.H., et al., *Toxic epidermal necrolysis following combination of methotrexate and trimethoprim-sulfamethoxazole.* Int J Dermatol, 2000. **39**(8): p. 621-3.
95. Criado, P.R., *Adverse Drug Reactions.* Dermatology in Public Health Environments: A Comprehensive Textbook, 2016: p. 519-576.
96. Ozmen, S., et al., *Probable cytarabine-induced acral erythema: report of 2 pediatric cases.* J Pediatr Hematol Oncol, 2013. **35**(1): p. e11-3.
97. Farr, K.P. and A. Safwat, *Palmar-plantar erythrodysesthesia associated with chemotherapy and its treatment.* Case reports in oncology, 2011. **4**(1): p. 229-235.
98. Burgdorf, W.H., W.A. Gilmore, and R.G. Ganick, *Peculiar acral erythema secondary to high-dose chemotherapy for acute myelogenous leukemia.* Ann Intern Med, 1982. **97**(1): p. 61-2.
99. Werbel, T. and P.R. Cohen, *Topical Application of 5-Fluorouracil Associated with Distant Seborrheic Dermatitis-like Eruption: Case Report and Review of Seborrheic Dermatitis Cutaneous Reactions after Systemic or Topical Treatment with 5-Fluorouracil.* Dermatology and therapy, 2018. **8**(3): p. 495-501.
100. Suvirya, S., A. Agrawal, and A. Parihar, *5-Fluorouracil-induced bilateral persistent serpentine supravenous hyperpigmented eruption, bilateral mottling of palms and diffuse hyperpigmentation of soles.* BMJ case reports, 2014. **2014**: p. bcr2014206793.
101. Geddes, E.R. and P.R. Cohen, *Antineoplastic agent-associated serpentine supravenous hyperpigmentation: superficial venous system hyperpigmentation following intravenous chemotherapy.* South Med J, 2010. **103**(3): p. 231-5.
102. Jamalpur, I., H.R. Mogili, and A. Koratala, *Serpentine supravenous hyperpigmentation.* Clinical case reports, 2017. **5**(9): p. 1546-1547.
103. Gould, J.W., M.G. Mercurio, and C.A. Elmets, *Cutaneous photosensitivity diseases induced by exogenous agents.* J Am Acad Dermatol, 1995. **33**(4): p. 551-73; quiz 574-6.
104. Kreidieh, F.Y., H.A. Moukadem, and N.S. El Saghir, *Overview, prevention and management of chemotherapy extravasation.* World journal of clinical oncology, 2016. **7**(1): p. 87-97.
105. Fraser, M.C. and M.A. Tucker, *Second malignancies following cancer therapy.* Seminars in Oncology Nursing, 1989. **5**(1): p. 43-55.
106. Chevallier, P., et al., *Results from a clofarabine-busulfan-containing, reduced-toxicity conditioning regimen prior to allogeneic stem cell transplantation: the phase 2 prospective CLORIC trial.* Haematologica, 2014. **99**(9): p. 1486-1491.
107. Jalaeikhoo, H., et al., *Acute Myeloid Leukemia as the Main Cause of Pancytopenia in Iranian Population.* Iranian journal of pathology, 2017. **12**(3): p. 265-271.
108. Kebriaei, P., et al., *Intravenous Busulfan Compared with Total Body Irradiation Pretransplant Conditioning for Adults with Acute Lymphoblastic Leukemia.* Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, 2018. **24**(4): p. 726-733.

109. Hsieh, P.-M., K.-C. Hung, and Y.-S. Chen, *Tumor lysis syndrome after transarterial chemoembolization of hepatocellular carcinoma: case reports and literature review.* World journal of gastroenterology, 2009. **15**(37): p. 4726-4728.
110. Howard, S.C., D.P. Jones, and C.H. Pui, *The tumor lysis syndrome.* N Engl J Med, 2011. **364**(19): p. 1844-54.
111. Au, E. and P.T. Ang, *Management of chemotherapy-induced neutropenic sepsis--combination of cephalosporin and aminoglycoside.* Ann Acad Med Singapore, 1993. **22**(3): p. 319-22.
112. Gamis, A.S., et al., *Alpha hemolytic streptococcal infection during intensive treatment for acute myeloid leukemia: a report from the Children's cancer group study CCG-2891.* J Clin Oncol, 2000. **18**(9): p. 1845-55.
113. Boztug, H., et al., *Antibiotic prophylaxis with teicoplanin on alternate days reduces rate of viridans sepsis and febrile neutropenia in pediatric patients with acute myeloid leukemia.* Annals of hematology, 2017. **96**(1): p. 99-106.
114. Al-Benna, S., C. O'Boyle, and J. Holley, *Extravasation injuries in adults.* ISRN dermatology, 2013. **2013**: p. 856541-856541.
115. Boschi, R. and E. Rostagno, *Extravasation of antineoplastic agents: prevention and treatments.* Pediatric reports, 2012. **4**(3): p. e28-e28.