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DRUGS USED TO TREAT SIDE EFFECTS OF CHEMOTHERAPEUTIC AGENT

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ABSTRACT

Cancer incidences and death rates are rapidly increasing worldwide. Intensive efforts to discover new anticancer drugs continue and laboratory and clinical studies have suggested methods for the more effective use of available drugs. Chemotherapy is the most effective and widely used treatment in most types of malignancies. One of the characteristics that distinguish anticancer agents from other drugs is the frequency and severity of side effects at therapeutic dose. Drugs affect these tissues in a dose dependant manner and there is individual susceptibility also. So toxicities are more frequently associated with these tissues. The side effects may be acute or chronic, self-limited, permanent, mild or potentially life threatening. This article aims to emphasize the management of these side effects. The most common side effects experienced are nausea and vomiting, anemia, hair loss, bleeding (thrombocytopenia), hyperuricemia, bone marrow depression, alopecia and mucositis. So different parameters must be taken into consideration to prevent, reduce and overcome these side effects. important to focus on research within this field in order to detect the proper ways which can help to overcome these side effects. Now a day's various treatment strategies were practically implemented to diminish the side effects. Proper management of toxicities is most importance because it affects the course of treatment and outcome of the patient in his physical, mental and social wellbeing.

KEYWORDS: Cancer cells, Chemotherapy,drug

Cancer cells are fast growing cells and the chemo drugs are used to kill these fast-growing cells. The chemo drugs will act throughout the body and affect healthy cells too. Damage of the healthy cells generates side effects. Chemotherapy is a method after surgery or radiation to obliterate any remaining cancer cells. Therapeutic effects are provided by different ways. Most of the chemotherapeutic agents destruct the DNA within cancer cells, preventing them from dividing (Rose, 1967). Chemotherapy possibly affect the mucous membranes throughout the body, include inside the mouth, stomach, throat. This leads to mouth sores and diarrhea. Additional to that hair follicles also getting damage lead to hair loss (http:// www.cancercare.org.). Chemotherapeutic agents producing side effects in various systems. Common side effects are anaphylaxis, pancytopenia, hepatotoxicity, ototoxicity, cardiotoxicity, nausea and vomiting, diarrhea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, and asthenia. Acute toxicity is prominent after therapy which are usually reversible and long-term toxicity, which are irreversible. This is how the morbidity and mortality of treatment increasing (George and Craig, 2010). Many side effects become few after treatment ends, but some may take months or even years to get out of that. The duration to get over some side effects and get energy back varies and it depends on many factors, including the drugs were given and overall health. It is important to focus on research within this field to manage in a proper ways to overcome these side effects.

MAJOR SIDE EFFECTS AND MANAGEMENT

Gastrointestinal Toxicity

Chemotherapy-induced nausea and vomiting has been cited as the most concerning symptom after administration of chemotherapy (Coates *et al.,* 1983). Chemotherapy induces the release of serotonin from the enterochromaffin cells which is present in the lining of the gastrointestinal tract. When an antiemetic drug is administered the serotonin stimulates type-3 vagal afferent serotonin receptors (5-HT3) which present in the gastrointestinal tract, the nucleus tractu solitarius of the medulla oblongata and the chemoreceptor trigger zone which lies exterior to the blood-brain barrier sends impulses to the vomiting center (ASHP, 1999). Chemotherapeutic agents are classified into highly emetic, moderately emetic, mild emetic according to their emetic potential (Rittenberg, 2002).

Oral disease is common in subjects undergoing chemotherapy. The mucosa can be secondarily infected, if once ulcerated rendering a portal for systemic infection (Main *et al.,* 1984). The normally proliferating epithelial lining get destructed and renewal of mucosal lining is slowed. This leads to conditions likes oral ulceration,

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dysphagia, stomatitis, diarrhoea, oesophagitis, & proctitis with pain and bleeding (Sharma *et al.,* 2005). Once treatment ends, mouth sores do disappear immediately. It's important that every patient should seek medical attention with health care team to manage this side effect of cancer treatments, including chemotherapy (http:// www.cancercare. org).

Constipation may also develop in patients who have received neuro toxic chemotherapeutic agents. Decreased bowel motility due to intra abdominal disease, hyper calcemia or dehydration can also contribute to constipation (Diana, 2001). A bowel regimen consists of initial mild stool softeners and bulk laxatives and then proceeding to stimulants or osmotic laxatives. Two of the most potent laxatives acceptable for long-term use are Lactulose & Sorbitol. Glycerine suppositories and Bisacodyl suppositories are stool softeners.

Diarrhea can be a major effect of treatment discontinuation and shows decreased drug efficacy because it represents a dose limiting toxic event. Diarrhea usually resolves within few days of post therapy with sorafenib and is often observed during the first treatment cycle with oral anti-EGFR tyrosine kinase inhibitor compounds (Motzer *et al.,* 2006).

Drugs causing vomiting: Docetaxel, Paclitaxel, Carboplatin, Oxaliplatin, Doxorubicin, Imatinib, Cytarabine, Cyclophosphamide, Ifosfamide.

Management

Serotonin (5-HT3) receptor antagonists (Roila *et al.,* 2010)

- Ondansetron .Oral: 24 mg, i.v.: 8 mg or 0.15 mg/kg
- Granisetron, Oral: 2 mg, i.v.: 1 mg or 0.01 mg/kg
- Tropisetron, Oral or i.v.: 5 mg
- Dolasetron Oral: 100 mg,i.v.: 100 mg or 1.8 mg/kg
- Palonosetron i.v.: 0.25 mg
- Dexamethasone, Oral: 12 mg, Oral: 20 mga
- Aprepitant, Oral: 125 mg

For low emetic potential drugs, corticosteroid and an antiemetic drug are used. High dose Metoclopramide functions both as a D2 receptor antagonist and 5-HT3 receptor antagonists and has significant antiemetic action (Peterson and Shubert, 2001).

Aprepitant (Emend) is a NK-1 inhibitors it acts on the vomiting center of the brain to prevent nausea and vomiting caused by chemotherapy. It blocks the action of substance P that stimulate nausea and vomiting reflexes. Aprepitant can be given as combination with serotonin antagonists and corticosteroid. It is available as a capsule, it should be taken before chemotherapy session and for two days afterward (http:// www.cancer.org.).

For a number of years, dronabinol tablet is prescribed as an antiemetic drug. In 2006, the U.S. Food and Drug Administration approved nabilone (Cesamet) tablets, which can be used as an antiemetic drug who have not been adequately helped by other antinausea medications (www.cancercare.org/copayfoundation).

Anti-anxiety drugs such as lorazepam (Ativan and others) or diazepam (Valium and others) are used to help block nausea and vomiting. These sedatives can be given intravenously and in pill form (2).

Drugs causing diarrhea- Docetaxel, Paclitaxel, Oxaliplatin, Gefitinib, Erlotinib, Bortezomib, Sunitinib, Cytarabine.

Management

- Loperamide 4 mg initially taking 2 mg, after each subsequent bowel movement, to a max dose of 8 mg in 24 h.
- Codeine phosphate 30 mg instead of loperamide or added to loperamide when control is not achieved with loperamide alone.
- Octreotide 100150 mcg injected 3 times daily up to 500 mcg (Benson *et al.,* 2004).

Hair Follicle Toxicity

Hair loss (alopecia) is a common and visible side effect of chemotherapy (Breed *et al.,* 2011). Alkylating agents (ifosfamide), topoisomerase inhibitors (etoposide), antimicrotubule agents (docetaxel, paclitaxel), anthracyclines (daunorubicin), and are known to cause the most severe chemotherapy induced alopecia. Hair loss is high when chemotherapy agents are administered intravenously, particularly when they are administered in combination (Paus *et al.,* 2013). Hair loss occurs because chemotherapy agents are designed to disrupt the mitotic and metabolic process of cancer cells. Rapidly dividing cells such as hair follicles are greatly affected. The rapid hair

growth, as well as high blood flow disturbs the normal hair-follicle cycling, causes breakage of the hair shaft and hair shedding (Batchelor, 2001).

Management

Scalp cooling is a supportive care intervention being utilised in many cancer centre's to reduce CIA. Scalp cooling method is evolved from the frozen caps which required frequent changes (e.g. PenguinTM Cold Caps). For the continuous cooling of the scalp require super-cooled liquid gel caps (e.g., Dignitana Dignicap, Paxman Orbis). Vasoconstriction reduces blood flow to hair follicles during peak plasma concentrations of chemotherapy agents, which in turn reduces its cellular uptake (Komen *et al.,* 2016). This is the mechanism involved in chemotherapy induced alopecia. Efficacy of may be achieved when the scalp skin temperatures maintain below 18°C. There are number literature confirming that scalp cooling is an effective treatment (Protière *et al.,* 2002). The most commonly used drug is corticosteroid and it is administered as an injection intradermally into the skin, or applied topically as a cream, gel or ointment. Calcineurin inhibitors, immunotherapies, and hair-growth-stimulating solutions are the second line treatment. Local treatments are usually used for people who have limited hair loss. Systemic therapies are used for patients who have more extensive hair loss, or who have rapid development of alopecia (https://www.fda.gov).

Haematological Toxicity

Hematologic toxicity induced by chemotherapy is called cytopenia. Most Cytopenia is described as decreasing of all three types of blood cells including Red blood cells ,White blood cells specially neutrophils (Leukopenia-Neutropenia) and Platelets (Thrombocytopenia) (Lyman *et al.,* 2016). This condition is one of the most serious complications which can be led to mortality and morbidity directly or indirectly (Vadhan, 2009).

The severity of anemia seen in patients varies; it depends on the extent of disease and the effectiveness of treatment (Chemothearpy induced anemia incidence and treatment).

Management

The management of anemia resulting from the severity of myelosuppressive chemotherapy. Treatment options include hematinic, crystalloid, and RBC transfusion, administration of epoetin alfa, or a combination of options.

RBC Transfusions

Patients with normovolemic, but symptomatic, anemia should be assessed for iron, folate, or vitamin B12 deficiency and should receive appropriate replacement therapy to rectify the deficiency. RBC transfusions are the treatment choice in cancer patients with acute anemia, subsequent blood loss, when crystalloid infusions not adequately maintain intravascular volume, in those with unresponsive to iron replacement, and whom medical necessity does not allow adequate time for epoetin alfa to be effective (Koeller, 1998).

Epoetin Alfa

Erythropoietin is a hematologic growth factor that regulates the proliferation, maturation, and differentiation of RBCs. One of the largest study shows that, one group received placebo and other group eptoin alfa. Patients in the two chemotherapy arms received 150 u/kg of epoetin alfa in a frequency of three times weekly for 12 weeks and patients in the no-chemotherapy arm received epoetin alfa 100 U/kg three times weekly for 8 weeks. From this study it is concluding that patients receiving epoetin alfa had a significant increase in hematocrit compared with placebo-treated patients (Abels, 1993). Other dosing ranges of eptoin alfa may be considerd, including an extending dose of 80,000 units (Epoetin Alfa) SC every 2 weeks and 120,000 units once in every 3 weeks (Epoetin alfa. Lexicomp Online).

Darbepoeitin dose 2.25 mcg/kg SC every week (Egrie and Browne, 2001) a randomized trial compared weekly dosing at 2.25mcg/kg versus fixed dosing 500 mcg every 3 weeks in 705 patients Hb level below 11.1g/dL. Currently the NCCN panel recommends both schedules. The fixed dose of darbepoitin include weekly dose of 100mcg (Besarab *et al.,* 1998) a fixed dose of 200 mcg every 2 weeks and 300 mcg every 3weeks (Gaydarova *et al.,* 2017).

Neutropenia – In neutropenic patients chances of infection is very high. The development of fever in neutropenics require an emergency care. This is because neutropenics have lack of signs and symptoms, unusual site involvement, rapid progression of infection, unusual

infectious organisms (Furie *et al.*, 2003). Febrile neutropenia, is one of the major complication in neutropenic patients. Infection-related mortality can be reduced by dose reductions in elderly patients (Lyman and Kuderer, 2003).

Management

Colony-stimulating Factors –The myeloid growth factors, and granulocyte colony-stimulating factor (G-CSF), have the ability to reduce the incidence and severity of neutropenia and febrile neutropenia (Crawford *et al.,* 1991). prophylactic G-CSF is recommended when dose-dense or dose-intense chemotherapy has been shown to have survival benefit.

Management

Dose reduction of chemotherapeutic agents and alteration of frequencies are the first step to control CIT. If bleeding occurs or if platelet counts are <10,000/μL (or with platelet counts < 20,000/μL if the patient is febrile) prophylactic platelet transfusions are recommended (McManus and Weiss, 1984).To decrease the bleeding risk of patients, antifibrinolytic agents such as epsilon-aminocaproic acid or tranexamic acid have been used (Kalmadi *et al.,* 2006). Total daily doses of 2–24 g of epsilon-aminocaproic acid given in 3 or 4 divided doses. Tranexamic acid doses of 4–6 g/d given as 3 or 4 divided doses (Lonial *et al.,* 2005). The patients who were contraindicated to platelet transfusion can be given with thrombopoeitin agents.

Nervous System Toxicity

The incidence of neurotoxicity associated with chemotherapy is increasing because of greater use of high dose chemotherapy and newer drugs causing neurotoxicity used in combination weakening the barrier found with the brain (Macdonald, 1996). Drugs, such as platinum analogs, thalidomide, bortezomib, antitubulins (eg. vinca alkaloids, taxanes), have the common adverse effect of neuropathy (Cavaletti and Marmiroli, 2010).

Management

The neuroprotective agent include the adrenocorticotropic hormone analogue Org 2766, (Wen, 2005) the free radical scavenger amifostine, (Openshaw *et al.,* 2004) and the leukemia-inhibitory factor (LIF) (Davis *et al.,* 2005) showing beneficial effects in neuropathy. Studies indicating that specific neurotoxicity of oxaliplatin, the cold-induced dysesthesias, and muscle contractions. It is thought to be that a metabolite of oxaliplatin oxalate, causes the acute chelation of ionized calcium and magnesium precipitating a neuronal voltage-gated Na+ channelopathy. Researchers used calcium and magnesium infusions to prevent this toxic effect and diminished the sensori motor symptoms to a significant degree (Gamelin *et al.,* 2004) . One of the non-randomized study concluding that Glutamine, 10 g three times daily for 4 days, was neuroprotective agent in patients receiving high-dose paclitaxel. The investigators found that glutathione is the best agent for the prevention of oxaliplatin-induced neuropathy. It may show similar promise in reducing the neurotoxicity of other platinum-based chemotherapy (Cascinu *et al.,* 2002).The only effective therapy is discontinuation of the causative chemotherapeutic agent. Tricyclic antidepressant, anticonvulsant, high dose vitamins are used in drug therapy. Management by a cytoprotectant like Amifostine is promising. Barton *et al.*,, in his study (Bukowski, 1996) topical mixture of baclofen, amitriptyline, and ketamine are used to treat CIPN in a group of patients who had numbness, tingling, or pain associated with peripheral neuropathy while receiving or after having received neurotoxic chemotherapy (Barton *et al.,* 2011).

Urinary Tract Toxicity

It varies from renal tubular damage by Cisplatin and Methotrexate to haemorrhagic cystitis (10%) by cyclophosphamide (Stillwell and Benson, 1988). The Contact of bladder wall with toxic metabolites of cyclophosphamide leads to mucosal erythema, inflammation, ulceration, necrosis and a reduced bladder capacity (Weiss). The main symptoms are hematuria and dysuria.

Management

The Acrolein conjugator, MESNA (2-mercaptoethanesulphonatesodium) acts by binding to acrolein and result in a non toxic Thioether. The use of MESNA and hydration reduce the of bladder toxicity with Ifosamide or high dose Cyclophosphamide. Acetylcysteine is a sulfhydryl compounds also used for the same indication. Depending on the degree of toxicity, bladder irrigation, and fulguration and in rare instances cystectomy may be warranted.

Skin Toxicity

Antineoplastic drugs induced skin manifestations may due to chemotherapy or targeted therapy. Many chemotherapeutic agents cause dermatological toxicities including mucositis, alopecia, and onychodystrophy (Jatoi *et al.,* 2008).

Management

Tetracycline having better prevention in Epidermal Growth Factor Receptor-targeted agent-induced skin rash following treatment with chemotherapeutic agent (Van Cutsem *et al.,* 2007). The anti-inflammatory effects of tetracycline provide effective rash palliation. Topical vitamin K3 (Menadione) prevents erlotinib- and cetuximab-induced EGFR inhibition in the skin.

For mucositis treatmen start with routine oral care, use of mucosal coating agents and analgesics. Oral care includes removal of dentures, soft cleansing of the mouth and teeth, oral rinses with salt and baking soda. Mucosal coating agents like Topical kaolin/pectin, diphenhydramine, oral antacids and maltodextrin. Ice chips, topical local anaesthetic solutions, topical morphine sulphate in water, oral or intravenous analgesia with opioids. Topical viscous lidocaine is used for relief of the symptoms, but, severe mucositis requires systemic opioid analgesics.

CONCLUSION

The primary obstacles to the clinical efficacy of chemotherapy have been the toxicity to the normal tissues of the body. Rapidly proliferating tissues such as bone marrow, gastrointestinal tract, hair follicle etc are the major sites of acute toxicities. Now a day's various treatment strategies were practically implemented to diminish the side effects. Proper management of toxicities is most importance because it affects the course of treatment and outcome of the patient in his physical, mental and social wellbeing.

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