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REVIEW ARTICLE

A REVIEW UPDATED ON CHEMOTHERAPEUTICS

*Akanksha Chandra[1], Rajesh Kr. Soni[2], Upendra Sharma[1], Sanjay Kr. Jain[2], Prayag Yadav[2]

[1]Institute of Pharmacy, Department of Pharmaceutics, Bundelkhand University, Jhansi (U.P), India

[2]Institute of Pharmacy, Department of Pharmacognosy, Bundelkhand University, Jhansi (U.P), India

Corresponding author's Email Id: acshrishti@gmail.com

ABSTRACT:

Antineoplastic therapy aims at completely eliminating all neoplastic cells, by either surgical, radio therapeutic or pharmacological (administration of drugs) intervention. If this is not possible or feasible, the aim of therapy becomes palliative, that is, its purpose is to reduce the number of neoplastic cells, to improve the symptoms and, if possible, to prolong survival while maintaining an adequate quality of life. Neoplastic cells constitute a heterogeneous cellular population, with biochemical, morphological and immunological differences. Consequently, they evidence a widely varying sensitivity to antineoplastic drugs. Furthermore, not all the cells present in a given tumor are in the same phase in the cell cycle (generally, in the proliferative or in the rest phase). When a neoplasm is diagnosed, most of its cells have usually attained a phase of decelerated growth, because of vascularisation problems, of nutrient competitively problems, of lack of physical space, or of problems of other types. Many of the chemotherapeutic drugs are most effective on cells that are in their division process, and this means that, in principle, a large proportion of the neoplastic cells will be resistant to the effects of a given drug. The small-molecule drugs are the ones whose molecular weight is less than 1000 Daltons. The fastest growing cells in the body are present in skin, hair follicles and lining of the gastrointestinal tract and hence they are affected the most during chemotherapy. In this present review summarized knowledge of chemotherapy by different way.

Key words: chemotherapy drugs, oral manifestations of chemotherapeutics

INTRODUCTION:

Chemotherapy continues to play a crucial role in the modern management of cancer. Another name for chemotherapy is cytotoxic therapy. The cancer cells grow at a faster rate as compared to the normal cells. The basis on which most of the chemotherapeutic drugs work is that they target the fast growing cells in the body minimally disturbing the cells growing slowly. The basic aim of chemotherapy is to kill the cancerous cells with minimal damage to the other healthy cells in the body. The chemotherapeutic drugs have been categorized into different categories. The small-molecule drugs are the ones whose molecular weight is less than 1000 Daltons.The action of antineoplastic drugs is not selective for neoplastic cells, sothat they have quite considerable side effects that are mainly evident in cell lines expressing higher growth and replication rates. Furthermore, antineoplastic drugs may evidence a degree of selective toxicity on particular organs, mainly the lungs, the liver, the kidneys and the nervous system structures. They may (and do) also induce derangements in the replication and processing mechanismsof the cells involved in immune responses, so that their use leads to a state of immune depression facilitating the development of bacterial, viral and fungal infections. In the long run they also cause other forms of toxicity, such as mutagenicity and carcinogenesis.

Cancer and Chemotherapy:

Cancer is the condition where the cells in the body increase and divide beyond limit. These cells slowly start spreading to the nearby tissues and then into the blood stream. In the developed nations cancer holds second position for causing the death of the people. The increase in pollution has lead to an increase in the cases of lung cancer while the longevity of life has increased the cases of colon cancer; the picture today shows that oneout of every 8 women suffers from breast cancer. The treatment procedure of cancer includes radiations, medication and above all the use of chemotherapy for the destruction of the cancer cells[1].

Almost 75 years ago, the researchers explored the fact that cancer affects the mitochondria. We are aware that mitochondria obtain energy for oxidizing the sugar glucose. In a tumor cells the mitochondria stops functioning and the glucose is broken down in the absence of oxygen. We are aware that mitochondria obtain energy for oxidizing the sugar glucose. In a tumor cells the mitochondria stops functioning and the glucose is broken down in the absence of oxygen. This suppression of the mitochondria in the cancer cells alters the metabolism process and helps the cancer cells to grow, acting as resistance against much standard chemotherapy[2].

Recommendations for the prevention of hypersensitivity reactions to chemotherapeutic drugs:

Prevention of hypersensitivity reactions caused by antineoplastic drugs (from Weiss, modified)[3].

Premedication:

- Dexamethasone 20 mg p.o. 12 and 6 h before therapy, and 20 mg i.v. immediately before therapy
- Dexchlorphenyramine 6 mg p.o. or 5 mg i.v., with the same schedule as for dexamethasone
- Consider ephedrine sulfate 25 mg p.o. 1 hour before therapy unless the patient has unstable angina pectoris or is hypertensive

- Careful suppression (whenever possible) of any ß-blocking medicationthat might potentiate a reaction or hamper its management

Particular measures during therapy administration

- Maintain a venous access
- Arterial blood pressure monitoring (if available)
- Ensure that epinephrine and diphenhydramine for parenteraladministration are immediately available
- Keep the patient under observation for two hours after theadministration of the antineoplastic drug is finished

Different Categories of Chemotherapeutic Drugs:

Most of the chemotherapeutic agents destroy the cancer cells by targeting the DNA functions. The different categories of chemotherapy agents are all follows[4]:

1. Alkylating agents
2. Antimetabolites
3. Plant alkaloids
4. Anthracyclines
5. Antitumor antibiotics
6. Platinums
7. Taxanes

Alkylating Agents:

These are the oldest class of anticancer drugs which attack the negatively charged sites on the DNA (oxygen, nitrogen, sulfur atoms and phosphorous).

Antimetabolites:

The antimetabolites intervene with usual metabolic pathways and involve the use of folic acid for preparing fresh DNA. Antimetabolites inhibit DNA synthesis and helps in DNA repair. Methotraxate, 5-Fluorouracil (5-FU), Thioguanine, Cladribine and Fludarabine are some of the examples of antimetabolites used for treating leukemia, breast, head, neck, colon, pancreatic, esophageal, anal and bladder cancer, lymphoma and sarcoma.

Plant Alkaloids:

Plant alkaloids are obtained from plant materials and are redivided into four groups namely taxanes, vinca (vincristine, vinorelbine and vinblastine), and topoisomerase inhibitors (irinotecan and topotecan) andepipodophyllotoxins (Etoposideand Teniposide) alkaloids.

Anthracyclines:

These drugs are prepared from natural sources help in the formation of the free oxygen radicals which result in DNA constituents break up following inhibition of DNA synthesis. According to Johns Hopkins Medical Institutions[5], for around four decades anthracycline class of chemotherapeutics such as epirubicin, idarubicin, doxorubicin (Adriamycin) and daunorubicin have been used for the treatment of different types of cancer like sarcomas, carcinomas, leukemia and lymphoma.Researches are still on its way to strengthen the fact that it would be helpful to use DCA to sensitize the tumor cells to apoptosis and then expose the patient to chemotherapeutic drugs. Because in that case even the lower dose of chemotherapeutic drugs would prove effective as the tumor cells become weak and lose immunity[2].The major drawback of these drugs is cardiac toxicity.

Antitumor Antibiotics:

Antitumor antibiotics work on the same line as that of anthracyclines.Example of antitumor antibiotics includes Bleomycin used for treating Hodgkin's lymphoma and testicular cancer.

Platinums:

Platinums include the use of natural metal derivatives in order to fightagainst cancer. These agents help in cross-linking the DNA subunits that helps in DNAsynthesis, transcription and function. Examples of platinums include cisplatin (first-generation platinum), carboplatin (second generation platinum) and oxaliplatin (third generation platinum).

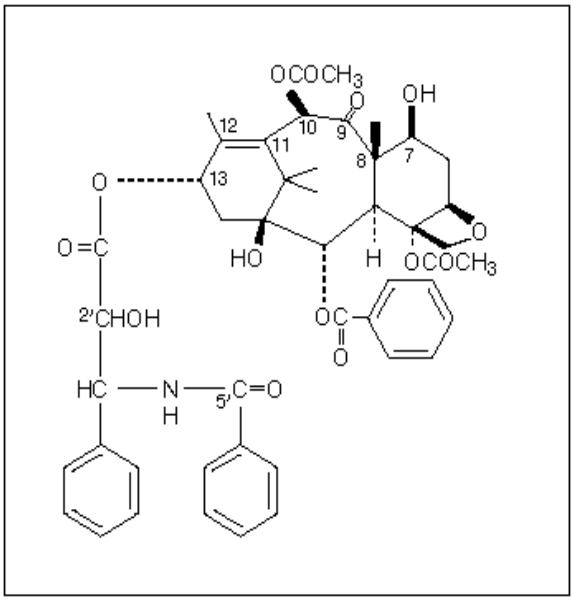
Taxanes:

The taxanes are new class of anticancer agents exerting their cytotoxic effectson the cancer cells though an exceptional procedure.

Taxol or Paclitaxel

Taxol or Paclitaxel, first taxane in clinical trials, is used in the treatment of testis, lungs,head, neck, lung and metastatic breast cancer. It is generally considered refractory toconventional chemotherapy and hence has been approved in the U. S. and other nations intreating patients with ovarian and breast cancer, which resist chemotherapy. This hasbeen approved as the palliative therapy.The tree is a scarce and slow-growingevergreen tree found in the forests of the Pacific Northwest and is also found to havecytotoxic effect against different tumors[6].

Structure of Taxol[7]



Mode of Action of Taxol

Polymers of tubulin are present in microtubules with alpha and beta protein subunits present in the tubulin heterodimers. The microtubules performs some crucial functions like formation of the mitotic spindle during the cell division and other interphase functions like maintaining the shape, signal transmission, motility and intracellular transportation[8,9,10,11]side effects may include:

1. Optic-nerve disturbance and scotomata.

2. Transient myalgia

3. Myopathy

4. Transient asymptomatic bradycardia[12]

5. Bradyarrhythmias like Mobitz type I and type II.

6. Third degree heart block

7. Fluid retention

8. Allergy

9. Hair loss

10. Anemia

11. Low platelet and white blood count

12. Allergic reaction

13. Nerve destruction

14. Diarrhea

15. Soreness of mouth with difficulty in swallowing

16. Skin infection

17. Myocardial infarction

18. Cardiac ischemia

19. Atrial arrhythmias

Vaccines Along with Chemotherapy

Cancer vaccines to control cancer growth and stop people from becoming victim of the disease are also being developed. Although, the research is only at its initial stage but is sure to give some fruitful results soon. These vaccines are being prepared by using not just a particular cell protein that is antigen but the entire cancer cell for preparing the vaccine. The cancer cell may be from the patient's own body, or it may be another person's cell. It can also be the one grown in the laboratory. Some vaccines are notsuitable to be given along with the chemotherapy[13].

Limitations of Chemotherapy

The adverse effects of chemotherapy include neurological problems, stress, emotional imbalances, depression, physical and emotional disorders of the heart. In women chemotherapy may lead to bleeding, bruising, infections and anemia. When chemotherapy is given to the patient it leads to the destruction of all types of cells along with the cancer cells, which are red blood cells, white blood cells and platelets. Hence, there is a heavy loss of all types of cells from the body and the body is more likely to become a victim of infections and experiences weakness during and post chemotherapy. It is therefore preferable to have the laboratory data of the patient before beginning with chemotherapy.The patient may experience dryness of mouth, sticky saliva and dark yellow urine with reduced urine output. These signs indicate dehydration in the body and medicines are usually recommended by the doctor to control them. Dryness in the vaginal area may also be seen in women with a decreased crave towards sex and alteration in their emotional and physical fitness.

Oral Manifestations of Chemotherapy:

Chemotherapeutic drugs are administered systemically over several weeks or months in a sequence of "treatment rounds or courses." This schedule allows some recovery of healthy tissues between each treatment of the toxic drugs.

Mucositis and ulceration

The gastrointestinal (GI) mucosa, because of its high cellular turnover rate, is highly susceptible to the toxic effects of many chemotherapeutic agents. Inflammation and ulceration of the mucosal lining of the mouth, pharynx, esophagus and the entire GI tract may occur. The patient may experience pain, nausea, vomiting and diarrhea.

Pain

Oropharyngeal pain is a prominent and frequent sequel of chemotherapy- induced mucositis. Descriptions of pain by patients do not always correlate with severity of tissue injury as assessed upon clinical examination.

Infection

Many drugs and some malignancies can suppress bone marrow production and induce leukopenia, which can result in increased risk of infections. The usual clinical signs of inflammation (redness, pain, swelling, heat) may not be present during periods of significant immunosuppression. If pain is present, the symptomatic areas of possible infection (operculum, periodontal pockets or mucosal ulcerations) should be cultured if the patient develops a fever of unknown origin. Infection may be caused by organisms usually found in the mouth such as Candida species, herpes viruses, streptococci and staphylococci.

Oral Manifestations of Chemotherapy Bleeding

Reduction of platelets (thrombocytopenia) and other clotting factors during periods of bone marrow suppression are the major causes of bleeding. Transfusion of platelets and/or clotting factors in conjunction with topical agents may be necessary for control.

Xerostomia/Salivary gland dysfunction

Patients may complain of decreased or thickened saliva. The duration of xerostomia is associated with the length of therapy, other prescribed medications and the health of the patient. Xerostomia may result in a lowered pH, alterations in the constituents of the saliva, and it may lead to rampant dental caries. A dry mucosa is more susceptible to pain, infections and irritation.

Taste alteration

Transient alteration in taste is common after the administration of some chemotherapeutic drugs.

Neurotoxicity

The patient may present with numbness or constant, deep pain that is often bilateral and frequently mimics toothache (odontalgia), but noodontogenic or mucosal source can be found. This phenomenon may be present after the administration of drugs such as vincristine and vinblastine.

Dental developmental abnormalities

Chemotherapy administered during dental development in childhood may cause shortened or malformed roots, enamel defects, disturbance in crown development and eruption.

Radiation therapy:

Potential Oral Manifestations of Radiation Therapy to the Oropharyngeal and Salivary Gland Region

Acute	Chronic
Taste alterations	Salivary gland dysfunction
Salivary gland dysfunction	Radiation caries/demineralization
Mucositis/Ulceration/Pain	Trismus/TMD
Infection Soft tissue necrosis	-
Nutritional deficiency/Dysphagia Osteoradionecrosis	-
Developmental maxillofacial deformity	-

Factors that influence intensity and duration of the oral manifestations

- total dosage
- rate of radiation delivery
- fraction size
- field of radiation
- radiation source
- previous surgical intervention
- oral hygiene and dental status
- medical and nutritional status of patient
- tobacco and alcohol use

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In adults, cytotoxic chemotherapy became established in the1970s as a curative treatment in advanced Hodgkin's disease[14], non-Hodgkin's lymphoma[15], teratoma of testis[16] and as an adjuvant treatment for early breast cancer[17]. The initial results suggested the potential use of cytotoxic chemotherapy as a definitive treatment or as an adjuvant therapy in asymptomatic patients with the aim of improving survival. However, as stated by Braverman[18] and others[19,20] the early gains in a few tumour sites have not been seen in the more common cancers. For most patients, the use of cytotoxic chemotherapy is for the palliation of symptoms and to improve quality of life[21,] with prolongation of survival being a less important outcome.

Oesophageal Cancer

The survival for oesophageal cancer is less than 10% at5 years[22]. For every 100 newly diagnosed patients, onethird has metastatic disease (M1) at presentation (n ¼ 33). In the remainder (n ¼ 67), only 40% (n ¼ 26) are medically operable, and only 80% of these will have a curative procedure (n ¼ 21). Those who do not have an operation (n ¼ 67 _ 21 ¼ 46) are suitable for treatment by radiotherapy or a combination of chemotherapy and radiotherapy.

In a Cochrane review reporting seven RCTs and 1653 patients[23], preoperative chemotherapy in resectablethoracic cancers was not shown to have a role, but an MRC trial[24] and a recent meta-analysis[25] has confirmed a benefit for preoperative chemotherapy. A further Cochrane review[26]of combined chemotherapy and radiotherapy compared with radiotherapy alone

for esophageal cancer showed a significant absolute improvement in overall survival at 1 and 2 years for combined chemotherapy and radiotherapy of 9% and 8% respectively, and a 5% absolute reduction in local failure. It can be concluded that, when a non-operative approach was selected, then concomitant chemotherapy and radiotherapy were superior to radiotherapy alone. Chemotherapy, therefore,has a curative role in all patients except those who areM1 at presentation. This is likely to be an overestimate as data were only available for 2-year follow-up.

Stomach Cancer

Stomach cancer has a 22.6e24.8% 5-year survival[22], with surgery being the only established curative procedure. Meta-analyses in 1993[27] and 1999[28] suggested that adjuvant chemotherapy might produce a small survival benefit of borderline significance in curatively resected

Colon Cancer

Surgery is the only established curative treatment forcolon cancer, with chemotherapy used as adjuvant treatment. The IMPACT Group analysis in 1995 of three separate trials of 5-fluorouracil and leucovorin in Duke's B and C colon cancer showed an improvement in 3-year

Disease free survival of 9% and overall survival benefit of 5%[29]. A further meta-analysis in 1997 compared a no-treatment control with postoperative chemotherapy (excluding liver infusion) in resected colorectal cancer[22]. The overall survival benefit for chemotherapy was 5% for colon cancer and 9% for rectal cancer.

Pancreatic Cancer

Pancreatic cancer has a 5-year survival of just over 5%[22]. The impact of gemcitabine is still being evaluated, but a recent RCT showed a median survival of 5.4 months, and a progression-free survival of 2.2 months with gemcitabinealone. An objective response was seen in only 5.6% of patients, and overall survival at 24 months was about 5% [31].

Lung Cancer

Small-cell lung cancer Incidence: 19% of total (Australia) and 13% of total in the USA (SEER). Virtually all patients receive initial cytotoxic chemotherapy. The overall 5-year survival for small-cell lung cancer (SCLC) is 3.5%, or 2.5% in limited-stage disease and 1.2% in extensive-stage disease[37].

Rectal Cancer

Surgery is the mainstay of treatment, with chemotherapy and radiotherapy used as adjuvant treatments. Two RCTs show that the combination of radiotherapy and chemotherapy decreased local recurrence and increased overall survival compared with a no-treatment control[32,33]. The NSABP R-02 trial[34] showed that chemotherapy alone improved disease-free survival and overall survival, and that radiotherapy alone decreased local recurrence, but had no effect on disease-free survival or overall survival.

Anal Cancer

The combination of radiotherapy and chemotherapy for sphincter preservation is now standard management, except in advanced disease, in which abdomino-perineal resection is still required after radiotherapy and chemotherapy. In two RCTs[35,36], the addition of chemotherapy to radiotherapy gave a higher complete response rate and colostomy-free survival than radiotherapy alone, but there was no effect on overall survival.

Breast Cancer

The results of adjuvant chemotherapy have been published in several overview publications. In summary,chemotherapy reduces the rate of recurrence and improvessurvival for women with early breast cancer[37,38]. No RCTs have reported results of adjuvant chemotherapy in women aged 70 years or over, and any benefit in this age group is therefore not evidence based.

CONCLUSION:

Chemotherapy has an ability to treat widespread cancer as compared to radiation therapy and surgery which has a limited coverage. There are a number of chemotherapeutic agents that are divided into alkylating agents, antimetabolites, plant alkaloids, anthracyclines, antitumor antibiotics, platinums and taxanes. Other chemotherapeutic drugs include includehydroxyurea, thalidomide, dactinomycin, and asparaginase.

Now with the advancement in researches, the drug will be able to reach the tumor site within hours instead of normal 2 days time. Researches are still in progress to make them more and more effective with less and less side effects. Also, cancer vaccines are being developed to control cancer growth although the process is still at an initial stage of development.

The best example of the 'over-selling' of chemotherapy is in breast cancer, where chemotherapy was introduced as the example of the new cure for solid malignancies. InAustralia, in 1998, only 4638 of the 10 661 women with newly diagnosed breast cancer were eligible for adjuvant chemotherapy (44% of total). From our calculations, only 164 women (3.5%) actually had a survival benefit from adjuvant chemotherapy. In other words, on average, 29 women had to be treated for one additional woman to survive more than 5 years.

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