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COMPARATIVE STUDY OF CISPLATIN AND CISPLATIN WITH DOXORUBICIN

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ABSTRACT

Cisplatin or cis-diaminedicloroplatinum (II) a platinum based antineoplastic agent is prominent drug for treatment of many malignancies includes bladder, ovary, lung, testicular cancer. Its mechanism of action is its ability to crosslink withthe purine baseof Deoxyribonucleic acid (DNA). It interferes the DNA repair mechanism cause damaging of DNA, and subsequently induce apoptosis in cancer cells.However, major side effectsof cisplatin in treatment ofchemotherapy in cancerpatients are including myelosuppression, ototoxicity, gastrointestinal toxicity, renal toxicity etc. Doxorubicin (DOX)also known as Adriamycin is a type of chemotherapy drug. It's a naturalanthracycline antibiotic. It slows or stopthe growth of cancer cell by blocking an enzymecalled Topo-isomerase 2, which isrequire for growth and division of cancer cells. Sideeffects canbe different person to person. They also depend on what other treatmentsyou're having. Many studied show combination treatments of cisplatin and doxorubicinshowed significant activity in basal cell carcinoma and squamous cell carcinoma.

Key words: *chemotherapy, cisplatin,doxorubicin,monotherapy, radiation, toxicity.*

INTRODUCTION

Cancer is a chronic disease which is a leading cause of morbidity and mortality worldwide. It is estimated that there will be 13.1 million deaths due to cancer in 2030[1]. Based on the most recent estimates of global mortality data (2019), more than three-quarters of the 20.4 million premature deaths (occurring at the ages of 30-70 years) are due to noncommunicable diseases (NCDs).For every 10 persons who die prematurely of Non-communicable diseases (NCDs), 4 die of cardiovascular disease (CVD), and 3 die of cancer so canceris leading causes of premature death as per World Health Organization (WHO) data [2]. Cisplatin (*cis*-diamine dichloroplatinum(CDDP) is platinum-based drug used in the treatmentof many cancers, including those of the head, neck, lung, testis, ovary and breast etc. the dose-limiting side effect of cisplatin is nephrotoxicity [3]. Cisplatin works via non-cell cycle-specific cytotoxicity, which is done through the covalently binding of platinum to the purine bases guanine and adenine. The intra- and inter-strand crosslinks created by this covalent interaction eventually result in strand breakage. While DNA repair mechanisms are going on, cells often undergo apoptotic or non-apoptotic cell death due to remnant damaged DNA, Ribonucleic Acid (RNA), and proteins. Cisplatin chemotherapy is particularly effective at targeting rapidly dividing cells, as appreciated in rapidly growing malignant tumors.The drug is excreted through urine, with 10% in the bile. Its terminal half-life is 24 hours, and its initial half-life is roughly 20 to 30 minutes [4]. Doxorubicinhas been the prominent drug of cancer therapy since long. Despite its broad-spectrum antineoplastic activity, adverse events particularly cardiotoxicity, has limited the use of conventional doxorubicin in clinical practice [5]. This was especially in patients with advanced disease needed for dose escalationDoxorubicin hydrochloride (HCl) liposomal injection was the first liposomal encapsulated anticancer drug to receive clinical approval and has activity against a number of malignancies including solid tumours in aftermath.Research in the past few years has concentrated on creating unique liposomal formulation. The exact mechanism of action of doxorubicin is intricate and still not clear. Doxorubicin interacts with the DNA by intercalation and it inhibiting the macromolecular biosynthesis.This further inhibits the actions of the enzyme topoisomerase II, and unleased the supercoils in DNA for transcription. Doxorubicin stabilizes the topoisomerase II complex after it has broken the DNA chain for replication, inhibiting the DNA double helix from being resealed and thereby stopreplication. Another mechanism of doxorubicin HCl is its ability to generate free radicals that induce DNA and cell membrane damage[6]. Doxorubicin is most common drug used in treatment of cancers of the bladder, breast, stomach, lung, ovaries, thyroid, soft tissue sarcoma etc. The most used doxorubicin-containing regimens may include Adriamycin, cyclophosphamide (AC), Taxotere, AC, Adriamycin, bleomycin, vinblastine, dacarbazine, bleomycin, etoposide, AC, vincristine etc. Doxil is mainly used for the treatment of ovarian cancer where it has progressed or recurred after platinum-based chemotherapy, or for the treatment of AIDS-related Kaposi's sarcoma.

ECONOMIC BURDENS

A. Cisplatin

Cisplatin is a widely used chemotherapy drug in the treatment of various type of cancers, but it is also associated with significant rates of ototoxicity as side effects. The study calculates the possible financial impact of using cisplatin as chemotherapy. Medication to cisplatin exists that it is as efficacious without the risk of hearing loss, and that the alternative treatment is no more expensive than current practice [7]. It was estimated that administering this genetic test to every paediatric cancer patient for whom cisplatin is first-line therapy. This might potentially save society expenditures per tested patient by an average of $71,168. This equates into possible yearly present value savings for British Columbia of over $2.4 million and for Canada of over $19.6 million [8].

B. Doxorubicin

The doxorubicin market is likely to continue growing in the upcoming years, with significant global growth already underway. Chemotherapy drugs like doxorubicin are

commonly used to treat different kinds of cancer. These include lung cancer, breast cancer, ovarian cancer, and soft tissue sarcomas. The market is driven by the rising global incidence of cancer and the rising need for efficient cancer treatment alternatives [9]. And also, advancements in drug delivery systems with combination treatments are further fuelling the market growth.There are several obstacles to take into account, including the high expense of therapy, the development of substitute medicines, and possible pharmacological side effects. Despite these challenges, the increasing focus on personal choice of medicine and targeted therapies is predicted to create lucrative prospects for the Doxorubicin market in the coming years.The market for doxorubicin was estimated to be worth USD 0.9 billion in 2021 and is expected to increase at a compound annual growth rate (CAGR) of 5.8% from USD 1.1 billion in 2022 to USD 1.7 billion by 2030 [10].

THERAPEUTIC EFFECTIVENESS IN DIFFERENT TYPES OF CANCERS

A.Cisplatin in ovarian cancer

Eighty percent of women with ovarian cancer respond poorly to the first cell reduction surgery. This is followed by chemotherapy, usually a combination of paclitaxel and cisplatin[11]. Patients with advanced stages of ovarian cancer have a greater percentage rate of ovarian cancer recurrence among these 70% of patients who undergo this treatment. Even though resistance is common, cisplatin is now one of the most potent chemotherapeutic medications used to treat ovarian cancer. Cisplatin treatment for ovarian germ cell carcinoma results in good response rates [12]. Since the malignancy in the ovaries is the most lethal of all gynaecological cancers.Understanding the molecular pathways of chemotherapy resistance in ovarian cancer is essential to maintaining effective treatment and developing stop-chemo-resistance tactics.

B. Cisplatin in testicular cancer

Testicular cancer, or malignant tumours are most commonly found in between ages 20–40 of male and it has become more ubiquitous. Treatment of testicular cancer by cisplatin and other platinum-based compounds has become scientific breakthroughs in present scenario, thus increasing the patients' survival rate [13]. On the other hand, a lot of patients have platinum refusal, which causes recurrence of this kind of cancer. Since the mid-1970's, during that time platinum-based, antineoplastic drugs, were first introduced and cisplatin-based chemotherapy has produced high endurance in testicular cancer (TC) patients.Similarly, in individuals where the illness has spread widely. Regretfully, not every patient with testicular cancer is cured; some individuals with widespread cancer do not experience a long-lasting remission after their initial course of treatment and eventually pass away from the illness [14].

C. Cisplatin in head and neck cancer

Head and neck cancer (HNC) refers to malignant tumors whichoccurring in the topmost of aero-digestive tract; which include the lips, mouth, tongue, nose, throat, vocal cords, and part of the oesophagus and windpipe. HNC is ranked number eight among the most frequent types of cancers globally and its rate of more than 500,000 cases each year. It's interesting to note that squamous cell carcinoma, or unchecked proliferation or malignant cells beginning in the epidermis, is the classification given to more than 90% of head and neck malignancies [15]. As a first-line operational chemo-radiation therapy for HNC, cisplatin is typically given either before or after surgery. The most common treatment plan is known as the Radiation Therapy Oncology Group (RTOG) schedule, which combines conventional radiation with the administration of cisplatin at a dose of 100 mg/m2 on days 1, 22, and 43, respectively. Under the RTOG schedule, cisplatin can also be given at a preferred rate of 40 mg/m2 in addition to conventional or higher doses of radiation therapy. Furthermore, it has been determined that, when treating locally advanced head and neck cancer, cisplatin plus well-known chemotherapeutic medications like docetaxel and fluorouracil is most effective for induction therapy when compared to cisplatin plus fluorouracil [16].

D. Cisplatin in oesophageal cancer

One of the most effective and widely used anti-neoplastic drugs in clinical practice for the treatment of oesophageal cancer is cisplatin. Oesophageal cancer is ranked number nine among the most prevalent types of cancer and number six in mortality rates among all malignancies globally; with80 % of all cases death [17]. Although removing part of or the whole oesophagus is the first-line treatment in non-advanced stages; higher than 50% of patients are subject to cancer metastasis. Drug combination of cisplatin and fluorouracil has been used as a basic antidote for oesophageal cancer patients as well as for those experiencing reoccurrence or at advanced stages.

E. Cisplatin in lung cancer

It has been determined to be the primary cause of cancer-related deaths worldwide. Cisplatin is regarded as the most popular anti-neoplastic drug to treat non-small cell lung cancer (NSCLC). But cisplatin is also known to cause adverse effects and medication resistance, particularly when exposed over an extended period of time [18]. Combining cisplatin with other chemotherapeutic drugs such as paclitaxel, gemcitabine, docetaxeletc represents a basic method for initial treatment of NSCLC.

F. Cisplatin in breast cancer

One of the most common cancers to be detected in women is breast cancer (BC), with most victims being over 60. Cisplatin is used as the first-line agent for BC treatment. Treatment for BC has included radiation, surgery, chemotherapy, or any combination of these [19]. Although carboplatin has been used to treat breast cancer, cisplatin is still the most effective medication for treating breast cancer.

G. Cisplatin in cervical cancer

In developing nations, cervical cancer ranks second among the most common cancers and is the third leading cause of death for women.The standard treatment for people with elevated risk factors and/or prematurely undergoing surgery is cisplatin plus pelvic radiation [20]. According to a Phase III clinical trial by the Gynaecologic Oncology

Group, concurrent administration of cisplatin and paclitaxel is a typical method of treatment for advanced or recurrent uterine cervical cancer.

H. Cisplatin in prostate cancer

Ten percent of all malignancies in males are caused by prostate cancer (PC), often known as the male prostate. It is regarded as the second most frequent disease worldwide [21]. When combined with carboplatin and oxaliplatin, cisplatin chemotherapy is the first line of treatment because these platinum-based drugs interact with DNA to create DNA adducts in cancerous cells and promote programmed death.

DOXORUBICIN

A. Doxorubicin in ovarian cancer

In the US, ovarian cancer is the most common gynaecologic cancer cause of death. Standard first-line treatment includes surgical debulking and platinum-based chemotherapy, generally consisting of carboplatin with paclitaxel (C+P). Delivery of doxorubicin by this pegylated liposomal carrier increases the agent's circulating half-life from approximately 3 hours to 55 hours and alters its toxicity profile [22].

B. Doxorubicin in bladder cancer

Bladder cancer is one of the most common urogenital malignancies in male.Doxorubicinis one of the most effective drugs used in bladder cancer therapy.But cumulative cardiotoxicity and nephrotoxicity limit its clinical applications. Compared to systemic application, drugs given by intravesical therapy mainly reach the inside of the bladder, with little-to-no effect on other organs, such as the heart, liver,etc [23].

C. Doxorubicin in breast cancer

Worldwide, breast cancer is the leading cause of death for women. which represents 29% of all female cancers in the world. Chemotherapy continues to be the besttreatment forbreast cancer, along with surgery. The first line chemotherapy treatment protocol for breast cancer is using anticancer drugs doxorubicin, docetaxel, and paclitaxel. Doxorubicin, an anthracycline antibiotic, is used as a cytostatic drug in breast cancer chemotherapy, and has been studied for several decades [24]. However, Firstly, treatment with doxorubicin causes toxic side effects such as cardiotoxicity and hair loss.

D. Doxorubicin in lung cancer

Lung cancer accounts for 14% of all newly diagnosed cancers worldwide, making it the second most prevalent cancer diagnosis for both men and women. first-line chemotherapy treatment involves cisplatin and carboplatin and other associated chemotherapy drugs like paclitaxel, docetaxel, irinotecan, topotecan, and gemcitabine are often used, with doxorubicin (Dox) being among the most effective [25]. Even good even rateof patient's survival is significantfrom these combination-chemotherapy treatments, drug resistance and drug-related toxicity severely limit clinical outcomes.

E. Doxorubicin in multiplemyeloma

Multiple myeloma (MM) is a malignant neoplasm of plasma cells and accounts for approximately 10% of all hematologic malignancies. MM is characterized by the accumulation of malignant plasma cells in the bone marrowand the presence of a monoclonal immunoglobulin (M-protein) which is produced by the malignant plasma cells in the serum or urine or both [26]. The doxorubicin has long been considered one of the most active agents forMM. The mechanisms arethe antiproliferative effects of doxorubicin involve in the inhibition of DNA, RNA, and protein synthesis, leading to cell death.

RESULT

Doxorubicin and its combination therapy fare better overall in studies examining clinical significance, side effects, etc. with cisplatin. The majority of current research endeavours are directed on augmenting comprehension in each of these domains. Furthermore, efforts are focused on reducing DOX toxicity, creating inhibitors that stop DOX resistance from forming, and creating effective strategies to increase DOX efficacy throughout therapy.

DISCUSSION

The cisplatin and doxorubicin both are very prominent drugs for various cancers and present day its usage increase year by year. The cisplatin shows more monotherapy useand doxorubicin mostly combination therapy with other antitumor agents [27]. As compared with cisplatin plus doxorubicin andcisplatin monotherapy, its achieved similar rates of complete resection and survival among children with standard-risk hepatoblastoma. Doxorubicin can be safely omitted from the treatment of standard-risk hepatoblastoma [28]. Between June 1998 and December 2006, 126 patients were randomly assigned to receive cisplatin and 129 were randomly assigned to receive cisplatin plus doxorubicin [29]. In the cisplatin-alone group, the rate of total resection was 95%, while in the cisplatin-doxorubicin group, it was 93%. And both dugs show different side effects mostly different toxicity [30]. Particularly in cisplatin treated,many patients experience reoccurrence to such cancer due to platinum refusal.Additionally, black, tarry stools, blood in the urine or stools, burning, numbing, tingling, or painful sensations, changes in the frequency or volume of urine produced, coughing or hoarseness, trouble breathing, dizziness, drowsiness, a feeling of fullness in the ears, fever or chills, increased thirst, appetite loss, etc. are common side effects of cisplatin [31].

CONCLUSION

Cisplatin is primarily used to cause damage to DNA by blocking the creation of new cells and inducing apoptosis, which is then followed by a number of signalling cascades. Despite its anticancer qualities, cisplatin exhibits a number of toxicological consequences that decrease cytotoxicity.To counteract the toxic effects of cisplatin during therapy, novel therapeutic strategies have been developed. These include combination drug therapy with other compounds such as paclitaxel, doxorubicin, tegafur-uracil, and gemcitabine, as well as drugs formulated using nanotechnology to improve cisplatin drug delivery and

provide cancer patients with less toxic therapy. Doxorubicin inhibits the topoisomerase enzyme, which inhibits or stops the development of cancer cells. This enzyme is necessary for cancer cells to proliferate. Individual differences may exist in the side effects.They are also reliant upon the other therapies you are receiving. Numerous studies have demonstrated that combined therapies with doxorubicin and cisplatin were highly effective in treating basal cell carcinoma and squamous cell carcinoma.

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