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THE ADJUVANT CHEMOTHERAPY DRUGS: DEVELOPMENT AND MODALITIES OF DISPENSATION CASE OF UNIVERSITY HOSPITALS IN MOROCCO

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ABSTRACT

Cancer is a group of diseases characterized by the uncontrolled growth and spread of abnormal cells. The World Health Organization (WHO) projects that without immediate action, the global number of deaths from cancer will increase by nearly 80% by 2030, with most occurring in low- and middle-income countries. The most common treatments for cancer are surgery radiation, chemotherapy, hormone therapy, immune therapy and targeted therapy. In recent years, oncologists have been show that chemotherapy can be associated to other adjuvant treatments with the intention of improving the patients quality of life this type of treatment has been very successful in changing the psychic state of the patient as well as reducing pain, nausea and vomiting during chemotherapy. This study was performed to disclose the clinical impact relating to the use of adjuvant therapy that can accompany the patient during treatment in combination with chemotherapy.

KEYWORDS: Cancer, chemotherapy, adjuvant treatment.

INTRODUCTION

Chemotherapy is one of methods of anti-cancer struggle, as well as surgery and radiotherapy. This is a general treatment, released in the body for aims to destroy the malignant cells from the original tumor. These antineoplastic chemical substances differ to other molecules used

against cancers, that are close to physiological products such as hormones (Hormonotherapy) or as cytokines (Immunotherapy). Chemotherapy attacks all cells in the body during division, the treatment act particularly on cancer cells who divide more rapidly than normal cells. However, they are not spared and it causes second effects.[1]

The term supportive care designates all treatments that can accompany the patient throughout his illness, they correspond to certain treatments (effectively the medications), and also an organization around the patient with complementary care[2] all these care that can be said comfort which is intended to relieve the patient besides the traditional treatments that we use. In cancerology, they recover, and the list is not exhaustive.

-The chronic and intractable pain

-The venous access

-Nutrition, nausea and vomiting

-The psychological care

-The social accompaniment

-Functional rehabilitation.

The present study aims to evaluted the mechanism of action for different adjuvant treatments (FCH, antiemetics, corticosteroids, folinates, cytoprotective.) and to study the methods of dispensing these drugs usually administered the same conditions as cytotoxic.

I. ADJUVANT MEDICATIONS FOR CHEMOTHERAPY

The adjuvant chemotherapy drugs are all treatments that accompany the patient throughout his illness.[3] They are designed to improve the quality of therapeutic care in addition to consensual treatments used in cancerology.[4-5] There are many treatments adapted to calm chronic pain associated to cancer, reduce nausea and vomiting chemotherapy-induced, overcome haematological toxicity of drugs or even prevent most frequent serious side effects of molecules. It is then a question of chemoprotection.

➢ THE HEMATOPOIETIC GROWTH FACTORS G-CSF

The induced neutropenia is a predictable second effect of antitumor chemotherapy, may restrict the continuation of treatment.[6-8] The G-CSF ("Granulocyte Colony Stimulating Factor") filgrastim NEUPOGEN^{R}, lenograstim GRANOCYTE^{R}: are hematopoietic growth factors stimulating specifically the growth and development of the neutrophil lineage.

Filgrastim is a human G-CSF recombinant unglycosylated unlike lenograstim which is glycosylated because produced by cells of Chinese Hamster Ovary (CHO).

Pegfilgrastim NEULASTA^{R} is a covalent conjugate of r-methHuG-CSGF and molecule of polyethylene glycol (PEG) of 20 kD, this conjugation which brings the prolonged duration by decreasing renal clearance.

- **THE ERYTHROPOIETIN (EPO)**

Epoetin alfa and beta (epoetin alpha EPREX^{R}, darbopoïétin ARANESP^{R} alpha, epoetin beta NEORECORMON^{R}) is a recombinant glycoprotein composition whose amino acid (165aa) and carbohydrate (4 channels) is identical to that of the endogenous erythropoietin human. It stimulates the formation (multiplication and maturation) of erythrocytes from stumps cells in the bone marrow. It's observed an increase in the erythrocyte count, reticulocyte and hemoglobin levels. The alpha darbopoïétin has 5 chains N-carbohydrate whereas the endogenous EPO possesses only 3 and additional sugar residues in order to increase the half-life of elimination. The epoetin administration mode is essentially by subcutaneous injection: 1 or 3 weekly injection to EPREX^{R}, NEORECORMON^{R}, ARANESP^{R}. Another schema: one injection every 3 weeks for Aranesp^{R}. The clinical response should be evaluated after 9 weeks (time for share). In ineffectiveness case, stopping injections is advocated.

The injections are given in the limbs or in the anterior abdominal wall (injection sites vary). In case of the impossibility of using the subcutaneous route, the use of intravenous route in 1 to 5 minutes remains possible, contrary the perfusion is indicated against.

- **ANTIEMETICS**

-The Antiemetic (setrons: ZOPHREN^{R} Ondansetron, Granisetron KYTRIL^{R}, NAVOBAN^{R} tropisetron, dolasetron ANZEMET^{R}): their action on the prevention of nausea and vomiting due to chemotherapy is related to the antagonism of 5 HT3 serotonin receptors, localized on the peripheral neurons and on the central nervous system. The serotonin release in the small intestine is originally of vomiting reflexes by activation of vagal afferents HT3 receptor.[8]

- The Peripherals Dopaminobloquants Antiemetic (Domperidone MOTILIUM^{R}): they block dopaminergic receptors of the chemoreceptor zone located outside of hematoencephalic barrier.

- The Neuroleptics Antiemetic (Metoclopramide, alizapride PLITICAN^{R}): they belong to the substituted Benzamides of antidopamines class, are the modifiers digestive behavior and they prevent vomiting by blocking dominergiques sites.

-The Phenothiazines Antiemetics (metopimazine VOGALENE^{R}) are the anti-dopaminergic antiemetics (anti-apomorphine) who spend little the hematoencephalic barrier.

➢ **CORTICOSTEROIDS**

It is the anti-inflammatory steroid (dexamethasone, methylprednisolone SOLUMEDROL^{R}) acting in the primary or secondary inflammation in the acute stage of inflammation; they stabilize the lysosomal membrane during the proteolytic catabolic phase and increase the capillary tonus during the exsudative vascular reaction phase. In cancerology they are used for the preventive treatment of nausea and vomiting induced by emetogenic chemotherapy in association with granisetron and as coantalgique.

➢ **THE FOLINATES**

Calcium folinate is a racemic mixture in most of specialties. Only the form L (levogyre into 6S) is active, but the form D (dextrogyre into 6R) is present, except in the ELVORINE^{R} specialty. Calcium folinate permits to potentiate the cytotoxic activity of 5-fluorouracil by forming a stable ternary complex upon binding of antimétabololite with thymidylate synthase.[9-10] The Concomitant administration is required. Calcium folinate is also an antagonist of the methotrexate antifolate activity. It permits a resumption of the synthesis of folic derivatives, especially in non-tumor cells after exposure to the cytotoxic agent, called rescuing or "rescue". It is administered in case of particular toxicity for conventional doses of methotrexate and systematically after high doses.[11-15]

➢ **THE CYTOPROTECTIVE**

- URO-PROTECTOR (MESNA UROMITEXANR)

This is an antidote for acrolein, metabolite irritating the bladder mucosa, produced by the metabolism of oxazaphosphorines II of cyclophosphamide and ifosfamide type. It leads with acrolein to stable and soluble thioethers. Mesna acts also by forming the stable condesnsation products with intermediary metabolites.

The treatment duration with mesna must be equal to that with oxazaphosphorine augmented the necessary time so that the concentrations of urinary metabolites of cytotoxic descend to the infratoxic level.

- CARDIO-PROTECTIVE (DEXRAZOXANE CARDIOXANER)

Indicated for prevention of cumulative chronic cardiotoxicity related to the use of Doxorubicin and Epirubicin FARMORUBICINE^{R} in patients affected with advanced cancers and / or in patients metastasized having previously received the treatment comprising an anthracycline.[16-17] The dose-dependent cardiac toxicity observed during treatment with cytotoxic anthracyclines is mainly due to the relatively vulnerable oxidative aggression of myocardium by free radicals iron dependent. The Dexrazoxane, analogous of Ethylenediaminetetraacetic acid (EDTA), undergoes an intramyocardial hydrolysis giving rise to metabolite with opened cycles. These two molecules are chelating metal ions and prevent the formation of Fe3+-antracycline complex, thus preventing the production of cardiotoxic reactive radicals coming from these complexes.

The mode of administration is intravenous infusion for 15 minutes before administration of anthracycline. The dose posology equal to 20 times that of doxorubicin equivalent or to 10 times that of epirubicin.

- BONE PROTECTOR (BISPHOSPHONATES)

Sodium pamidronate, zoledronic acid ZOMETA^{R}: It is a strong inhibitor of osteoclast activity, and thus of bone resorption. In vitro, it inhibits the formation and dissolution of calcium apatite crystals. It prevents accession of osteoclast precursors to the bone and therefore their transformation into mature osteoclasts, able to resorb bone. However, the local and direct antiresorptive effect of bisphosphonate related to osseous screen, appears to be the predominant mode of action.

It delays or prevents bone complications and their consequences (hypercalcemia, fractures, recourse to surgery and bone irradiation, medullary compression) and decreases bone pain in patients affected with advanced myeloma stage, and used with anti-cancer treatment retards the appearance of secondary bone metastases of osteophilic cancers (breast, lung, thyroid, kidney, prostate.).

Chemoprotective pleiotropic (amifostine ETHYOL^{R}) is a prodrug which the thiol function is protected by a phosphate group. After dephosphorylation by membrane alkaline phosphatase, the active metabolite (WR 1065) enters preferentially in non-tumor cells as it exercises a protective effect overlooked of alkylating agents or platinum derivatives; by capturing the free radicals generated by cytotoxic.

II. STUDY OF THE DISPENSATION OF ADJUVANTS DRUGS FOR CHEMOTHERAPY

➢ MATERIALS AND METHODS

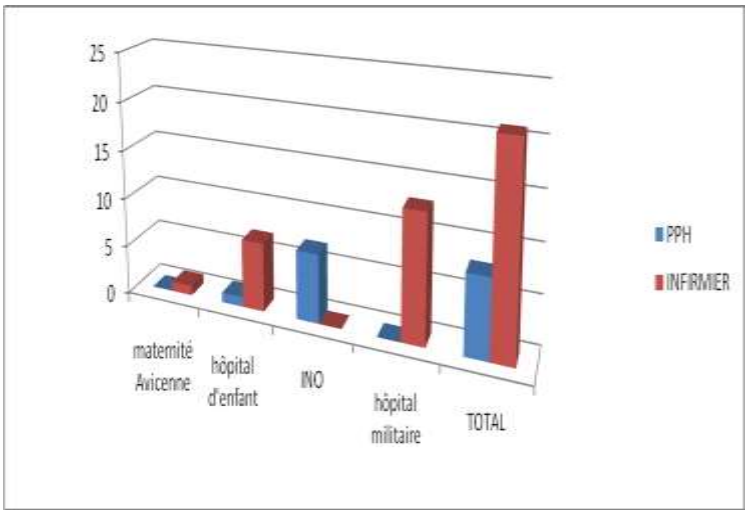
This is a survey on adjuvant chemotherapy drugs supported by qualitative and quantitative descriptive study on the methods of dispensing these drugs in hospitals of Rabat - Morocco (Child Hospital, Maternity Hospital, National Institute of Oncology and Military Hospital).

The population in this study is all staff exerting in dispensing and reconstitution units of patients with cancer, the sampling method is the reasoned choice. The method of data collection is a questionnaire.

All these institutions have pharmacy pole whose mission is to ensure the management the dispensation, the reconstitution of cytotoxic drugs and adjuvants for chemotherapy drugs in addition to the function of teaching and research.

➢ RESULTS AND DISCUSSION

This study concerns all the staff from the units, of dipensation and reconstitution of adjuvant drugs for chemotherapy at the university hospitals of Rabat. Among the highlights of this study; no similar studies have been conducted on this topic.



It is noted that the number of nurses is much higher than the number of PPH

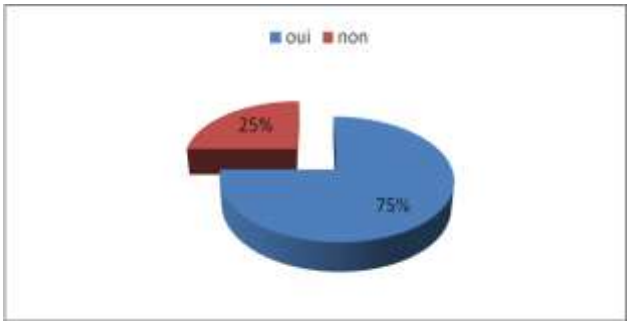
Figure 1: Distribution of staff according to the status in the management and dispensing units of adjuvant drugs for chemotherapy.

100% of the participants confirm that the management of adjuvant chemotherapy drugs is under the responsibility of a pharmacist

Figure 2: Responsibility for the management of adjuvant chemotherapy drug.

25% of participants confirm that the reconstitution and administration of adjuvant chemotherapy drugs is made in the same conditions as the anticancer drug

Figure 3: Reconstitution and administration of adjuvant chemotherapy drugs.



75% of participants manage adjuvant drugs for chemotherapy independently of anticancer drugs

Figure 4: The management of adjuvant chemotherapy drug.

The majority of staff is responsible for the reconstitution and administration of anticancer agents. The preparation of adjuvants anticancer drugs come in last place with a low percentage (18%).

Figure 5: Distribution of staff according to work stations.

CONCLUSION

For the adverse effects caused by cytotoxic that are variables and inconstant, are added the emotional, physical, mental and functional state of the patient. In practice, the anticancer treatment must be preceded by an essential and long evaluation time. Adjuvant treatments chemotherapy as they exist, are an integral part of the supportive care and chemotherapy protocols. Prepared and reconstituted in the same conditions as the cytotoxic. The adjuvant treatments well tolerated in general have shown a great interest for treatment of cancer patients. But Having regard to improve the safety and quality of dispensation of the drugs it would be desirable to manage them in the same conditions as anticancer drugs, activity regrettably limited to only one institution or hospital in Rabat.

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