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Anti-Cancer: Principles of use and Management of Side Effects

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Abstract **Short Communication**

Today, with the rapid progress we are seeing in the development of new cancer drugs, the importance of pharmacist in the interprofessional oncology team and in the pathway therapy for people with cancer. therefore, the control of principles of use and management of side effects turns out to be crucial. This short communication aims to present the essential points helping the pharmacist in his oncological clinical pharmacy activity.

Keywords: cancer drugs, cytotoxic drugs, interprofessional oncology, undifferentiated malignant cells.

INTRODUCTION

In Morocco, the national annual incidence of cancer is estimated at approximately 101 new cases per 100,000 inhabitants, which would correspond to 30,500 new cases of cancer each year. The incidence of breast cancer continues to increase, making it currently the most common cancer among women in our country [1]. The appearance of a tumor results from the anarchic proliferation of undifferentiated malignant cells that no longer respond to signals to stop cell division and apoptosis. It also acquires neoangiogenic and even metastastatic properties. Anti-tumor treatments can then involve surgery, radiotherapy or chemotherapy. Among anticancer drugs, cytotoxic drugs are not selective and their action on healthy cells is the cause of adverse effects (AEs) whose prevention and management, making it possible to improve patient tolerance and compliance, must be an integral part of their care [2].

Generalities

Anticancer drugs include drugs acting on all cells such as cytotoxics and cytostatics (e.g. hormonal treatments) as well as targeted drugs (e.g. monoclonal antibodies) [3].

They are mainly cycle dependent (e.g. alkylating), meaning they act on proliferating cells. Some are called phase dependent (e.g. taxanes) because they are only effective on cells in a given phase [4, 5] :

- **Action on the synthesis of nucleic acids:** These are antimetabolites like 5-FU and antifolics like methotrexate or ALIMTA. For the latter, the antidote, i.e. folinic acid, must be administered after chemotherapy. We talk about “rescue”.
- **Action on DNA structure:** These are alkylators, derived from nitrogen mustard such as cyclophosphamide (endoxan) or platinum salts as well as intercalants or inhibitors of topoisomerases I (irinotecan) and II (etoposide, anthracyclines). Their goal is to denature DNA to lead to cell death.
- **Action on mitosis : spindle poisons:** They inhibit the polymerization (vinca-alkaloids) or depolymerization (taxanes) of spindle tubules thereby preventing cell division.

Use principles

The handling of cytotoxic drugs requires strict compliance with good practices aimed at protecting both the preparations and the personnel, particularly through the centralization of this activity [6].

- **Goals**

The treatment can be curative by destroying the tumor cells. In this case, chemotherapy is called adjuvant when it completes the action of surgery or radiotherapy (e.g. colon cancer) or neoadjuvant when it precedes surgery or radiotherapy (e.g. lung cancer).

Treatment can be palliative when it aims to improve the quality of life and provide relief to the patient [7-10].

- **Differential toxicity**

Cytotoxics are non-selective. They are active on cells engaged in the cell cycle but tissues and tumors containing many multiplying cells are more sensitive to chemotherapy. They are therefore more toxic to cancer cells, and also have a lower regenerative capacity. Carrying out cures therefore allows healthy cells (particularly blood cells) to recover during periods between cures [11, 12].

- **Resistance**

A phenomenon of resistance to treatment may be observed, responsible for a reduction in effectiveness. It comes from a reduction in drug entry into the cell, an increase in its efflux systems, increased intracellular metabolism or even an alteration of the treatment target.

To combat this phenomenon, we can:
- increase the doses
- genetically select patients

ex: HER2+ for treatment with HERCEPTIN, K-ras for treatment with ERBITUX
- or by combining several molecules with different mechanisms of action

ex: FOLFIRI protocol with folinic acid + 5FU + irinotecan in colon cancer

This polychemotherapy should allow a gain in effectiveness without an increase in toxicity. It allows an addition or even a synergy of effects and reduces selection pressure and undesirable effects [13-19].

- **Multidisciplinary consultation meeting (MCM)**

Improving the quality of patient care requires the generalization of MCMs in which the pharmacist has a major role to play: creation of computer protocols by associating premedications and adjuvant therapies aimed at improving tolerance or potentiating the action of chemotherapy, prediction of specific treatments, pharmaco-economic study, etc.

These RCP must be recorded in the patient's file.

Therapeutic regimens are protocolized according to standards (Example: ACSO, INCa). Hospitals most often come together within regional networks to discuss their files and ensure a coherent care pathway for the patient.

These protocols make it possible to define the different lines of therapeutic strategy for a given cancer and to standardize prescriptions (details on the route, duration and frequency of administration). They are very often adapted according to the patient's body surface area (prescription in mg/m²), their renal clearance and their condition.

- **Validation**

Pharmaceutical validation is only carried out after medical validation. Pharmaceutical computer software allows the preservation of a patient history, making it possible to verify in particular the consistency of the therapeutic strategy and the space between treatments.

MANAGEMENT OF ADVERSE REACTIONS (AE)

They are graded according to the WHO from 1 to 4 depending on their severity. Their management is inseparable from the treatment [20].

- **Non-specific toxicity**

The action of cytotoxics on healthy cells is greater in rapidly dividing tissues (bone marrow, skin appendages and digestive mucosa). The first AE to appear is fatigue, responsible for numerous treatment discontinuations [11-12].

a- Digestive toxicity

Nausea and vomiting (NV) are the most feared. They vary depending on the molecules and from one patient to another. We distinguish the anticipated N/V which will be taken care of by anxiolytics; immediate (< 24 hours) or delayed (> 24 hours) N/Vs. The following will then be used: metoclopramide (PRIMPERAN) for low-emetogenic chemotherapies (CT) (5-FU); corticosteroids; setrons and aprepitant for strongly emetogenic CT as with cisplatin (SOLUMEDROL + ZOPHREN + EMEND).

b- Myelotoxicity

More frequent and early, its consequences are major. Before any treatment, the patient's recent CBC must be assessed.

Neutropenia is the most dangerous of hematological toxicities. If PN < 1G/L, the risk of infection must be taken into account. It can be prevented by injection of G-CSF (GRANOCYTE). In the event of febrile neutropenia, broad-spectrum antibiotic therapy will be started.

More rare, thrombocytopenia exposes you to a risk of severe bleeding. If Pq < 20 G/L, transfusion of platelet concentrates is systematic.

Anemia, which appears gradually over the course of treatment, can be prevented by injection of EPO with or without iron. If the Hb < 8g/L it will be treated by transfusion of packed red blood cells.

c- Mucocutaneous toxicity

Alopecia has a significant psychological impact (e.g. doxorubicin) for patients. Always reversible, it begins after 10 to 20 days with a maximum effect at 1-2 months. The use of cooling helmets has unpredictable effectiveness and is sometimes contraindicated.

Oral mucositis (e.g. 5-FU or anthracyclines) can be very painful and lead to postponement or reduction of treatment. Their prevention is based on rigorous oral hygiene and maintaining salivation. Their treatment is based on the use of mouthwashes (sodium bicarbonate, fungizone), anti-infectious and analgesic treatments, see KEPIVANCE.

Hand-foot syndrome is a frequent complication of 5-FU treatments. It manifests as erythema and burns which progress to necrosis. It is prevented by reducing exposure to heat and is treated with cryotherapy and emollient creams.

- **Specific toxicity**

a- Neurotoxicity

Spindle poisons, platinum salts and AVASTIN are responsible for peripheral neurotoxicity causing sensory damage and pain. These disorders, which gradually develop, alter the patient's quality of life. It can be prevented by the administration of Ca gluconate and Mg sulfate or treated symptomatically (tricyclic antidepressants, carbamazepine).

b- Nephrotoxicity

Cisplatin may be responsible for acute renal failure. Prevention is based on dosage adaptation based on the patient's renal clearance. Hyperhydration, before, during and after its administration, must be systematic. LASILIX can be used to restart diuresis.

Methotrexate nephrotoxicity is linked to the risk of intratubular precipitation. Hyperhydration associated with alkalinization of urine constitutes an effective prevention measure

Cyclophosphamide and ifosfamide present specific toxicity on the mucous membranes of the excreto-urinary tract linked to the formation of a toxic metabolite: acrolein. The main signs are hematuria and cystitis. Prevention is based on co-administration of mesna (UROMITEXAN).

c- Cardiotoxicity (anthracyclines, 5-FU, HERCEPTIN)

Irreversible and limiting, it requires monitoring of cardiac function. For anthracyclines, its prevention is based on the administration of CARDIOXANE and monitoring of cumulative doses.

- **Therapeutic education**

Patient must be made aware of these AEs to be able to prevent them (fever ⇔ neutropenia) and better understand them. This also allows for better compliance and therefore effectiveness of the treatment.

CONCLUSION

Anticancer drugs are an important class of drugs due to their impact on diseases that are the scourge of our society. Managing the adverse effects that they may cause is essential to guarantee quality care and good patient compliance. The pharmacist plays a major role here, without forgetting the obligations he has to secure the anticancer drug circuit.

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