**Ministry of Higher Education and Scientific Research**

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# "Study the recording adverse drug reaction of chemotherapy agents in pharmacovigilance center in Basra"

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## Abstract:

**Background**: The topic is on pharmacovigilance, which focuses on monitoring and identifying adverse drug reactions. Pharmacovigilance is defined as '…the activities involved in the detection, assessment, understanding, and prevention of adverse effects or any other drug related problems….' All drugs have the capacity to cause adverse effects and no drug is completely safe. The main goal of pharmacovigilance is thus to promote the safe and effective use of health products, in particular by providing timely information about the safety of health products to patients, health-care professionals, and the public. Cancer patients are prone to adverse drug reactions due to the complexity of the neoplastic disease and its treatment. Pharmacovigilance of anti-cancer medicines is further complicated because patients have comorbidities, as for elderly patients. It is even more challenging when complete safety and risk data for a drug are lacking, as may occur for new molecules or when it comes to drugs for children. The aim of our study is to report the adverse drug reactions of anti-cancer agents that used in oncology centers in Basra city. **Methods:** The data were collected for Pharmacovigilance Center in Basra and the collected data was for one year duration (Jan2022-Jan 2023). **Results:** nausea and vomiting were the highest percent 40.6%, diarrhea reported 11.9%, bone pain 8.9% **Conclusions:** pharmacovigilance center is necessary to record adverse drug reaction and important in order to react with any problem that can face medical team or effect on patient life.

## Introduction:

Pharmacovigilance is a critical component of modern medicine, with the ultimate goal of promoting the safe and effective use of medicines. Adverse drug reactions (ADR) represent a significant public health problem worldwide, and it is estimated that ADRs are the cause of as many as 5% of all hospital admissions. The identification, evaluation, understanding and prevention of ADRs is essential to minimize harm to patients, to improve medication safety and ultimately to enhance patient care. (1)

Pharmacovigilance involves the continual monitoring of drug safety throughout the entire lifecycle of a drug, from pre-clinical development to post-marketing surveillance. It encompasses a range of activities including adverse event reporting, signal detection, risk management and risk communication. Pharmacovigilance plays an integral role in identifying and mitigating risks associated with medications, including those that were undiscovered during clinical trials due to the limited sample size and duration. (2)

Although regulatory agencies such as the United States Food and Drug Administration (FDA) mandate post-marketing surveillance, pharmacovigilance and ADR reporting is the responsibility of all stakeholders in the healthcare system. This includes healthcare professionals, patients, drug manufacturers and regulatory authorities. Reporting of ADRs not only sheds light on the safety profile of a particular drug but can also lead to the identification of previously unknown risks and the development of measures to minimize these risks. (3)

In recent years, the role of pharmacovigilance has become increasingly important as medications become more complex, and the number of patients taking multiple drugs continues to rise. Developing and implementing effective pharmacovigilance systems is crucial to ensure patient safety and optimize the benefits of medications for all individuals. As such, understanding the critical role that pharmacovigilance plays in promoting drug safety, and how this can be achieved through effective ADR reporting, signal detection, and risk management is crucial for all stakeholders involved in patient care. (4)

## Methodology:

Our study, retrospective one, was made on the recorded data founded in Pharmacovigilance Centre in Basra City and was related to anti-cancer agents. The reported data was for one year duration (Jan 2022-Jan 2023) and involved treatment period, what are the most affected ages, methods of treatment, and what the most efficient treatment for ADR is.

The collected data lasts one month duration from 1/3/2023to 1/4/2023.

The statistical analysis was made by using Excel program

## Results

### Table 1: demographic data of recorded patients

In table 1, demographic data of collected patients data, involving age, gender, duration of hospital residence, etc…

Higher rate was reported in medical center for oncology, which took 95% of reported cases. Patients age divided into age groups and age group older than 60 years old was the higher percent (30.7%). Females were 52.5% while males were 48%. Almost patients received one chemotherapeutic agent (58.4%). All drugs were received parenterally.

| Parameter | Subcategories | No.(%) |
|---|---|---|
| **Oncology center** | Pediatric hospital for cancer | 5% |
| | Medical center of oncology | 95% |
| **Patient age (years)** | 0-10 | 5 (5%) |
| | 11-20 | 6(5.9%) |
| | 21-30 | 8(7.9%) |
| | 31-40 | 9(8.9%) |
| | 41-50 | 22(21.8%) |
| | 51-60 | 20(19.8%) |
| | More than 60 | 31(30.7%) |
| **Gender** | Male | 48(47.5%) |
| | Female | 53(52.5%) |
| **Duration of hospital residence** | 1-3 days | 68(67.3%) |
| | 4-6 days | 16(15.8%) |
| | More than one week | 17(16.8%) |
| **No of anticancer taken at same time** | One | 59 (58.4%) |
| | Two | 36 (35.6%) |
| | Three | 5 (5%) |
| | >three | 1 (1%) |
| **Is there any drugs (other than anticancer) in Rx?** | Yes | 52 (51.5%) |
| | No | 49 (48.5%) |
| **Rout of anticancer drugs** | Oral | 0 |
| | parenteral | 101 (100%) |

## Table 2: Types of Adverse Drug Reactions

In table 2, the reported adverse drug reaction in oncology centers reported by pharmacovigilance unit in hospital

| Adverse drug reaction | Percent |
|---|---|
| **Nausea and vomiting** | **41 (40.6%)** |
| **Diarrhea** | **12 (11.9%)** |
| **fever** | **8 (7.9%)** |
| **Bone pain** | **9 (8.9%)** |
| **fatigue** | **7(6.9%)** |
| **Hematuria** | **7(6.9%)** |
| **Loss of appetite, constipation** | **7 (6.9%)** |
| **Dizziness** | **6 (5.9%)** |
| **Dyspnea, anorexia** | **5 (5%)** |
| **Paresthesia, headache, skin rash** | **4 (4%)** |
| **Cough, weakness** | **3 (3%)** |
| **Miscellaneous, which include** | |
| **Chills, purple face, hair falling, dysuria, neutropenia, abdominal pain, hypotension, black skin, GIT bleeding, flushing** | **1 (1%)** |

## Table 3: Severity of the Reported Adverse Effect

In table 3, the reported adverse drug reaction with their degree of severity

| | | |
|---|---|---|
| Severity of the reported adverse effect | Mild | 89 (88.1%) |
| | Moderate | 1 (1%) |
| | Severe | 11 (10.9%) |
| | Lethal | 0 |

**Table 4: Anti-Cancer Drugs That Most Likely to Cause Adverse Drug Reaction**

In table 4, each anticancer drugs with the incidence of adverse drug reaction reported in oncology center

| Drug | N&V | Diarrhea | Fever | Bone Pain | Fatigue | Hematuria | Loss Appetite | Dizziness | Dyspnea | Anorexia | Headache | Thrombocytopenia | Skin Rash | Paresthesia |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Docetaxel®** | 1 | | | | | | | | | | | | | |
| **Leucovorin** | 1 | | | | | | | | | | | | | |
| **Fluorouracil** | 2 | | | | | | | | | | | | | |
| **Cisplatin** | 4 | 1 | | | | 2 | 1 | | | | | | | |
| **Carboplatin** | 7 | | | | | | 1 | 1 | | | | | 1 | |
| **Rituximab** | 1 | | 1 | | | 1 | 1 | 1 | | | 1 | | 1 | 1 |
| **Vincristine** | 2 | 1 | | | | | | | | | | | | |
| **Cyclophosphamide** | 1 | | | | | | | | | | | | | |
| **Paclitaxel** | 4 | 3 | 2 | 1 | | | 1 | | | | 1 | | 2 | 2 |
| **Gemcitabine** | 8 | 2 | | 5 | 2 | 1 | 2 | 3 | 2 | 3 | | 4 | | |
| **Oxaliplatin** | 5 | 2 | 1 | 1 | 2 | 2 | 1 | | 2 | 2 | | | | 1 |
| **Doxorubicin** | 5 | 3 | 1 | | 1 | | | | | | | | | |
| **Ifosfamide** | 1 | | 1 | | | | | | | | | | | |
| **Zoledronic Acid** | 2 | | 2 | 1 | 2 | 1 | 1 | 1 | | | 1 | | | |
| **Bevacizumab** | | | | | | | | | | | 1 | | | |

## Discussion:

Pharmacovigilance employs various methods to monitor the safety of medications with spontaneous reporting being the most common one. Spontaneous reporting is done by people who make a connection between a drug and a suspected drug-induced event. This data about suspected ADRs are collected in a central database. When a new medication is released in the market, information about its adverse effects becomes available, which may result in its withdrawal, restrictions in use and labelling changes. Some adverse effects are a cause of concern among healthcare professionals and the public. Data on drug efficacy and safety are usually based on the experience of thousands of people who participated in controlled clinical trials (1)

In table 1, demographic data of the patients were recorded. 101 case-sheets were reported in our study for period of one year. Almost reported cases in this period from Medical center of Oncology in Al-Sader Teaching Hospital, Basra (95%) and the remaining from pediatric center for cancer management. This can give a bad impact about prevalence of this disease among adult patients and how can they be suffering from disease and drug adverse effects, with highest percent in age group over 60 yrs. Such age group almost having other conditions, like hypertension, diabetes, cardiovascular diseases, and cerebrovascular accident (CVA).

Presence any of HT can cause global mortality and morbidity, so careful and accurate attention making for these patients' group (2)

Diabetes also carries a risk factor for getting cancer, that is because both diseases sharing the same risk factors, may have same pathways in certain points, and some anti-cancer therapy elevate blood glucose level which can worse DM symptoms and control (3)

Females have a higher percent of getting cancer (52.5%) comparing to that of males (47.5%), this result is mostly due to the higher percent of patients are from medical center of oncology and most cases here are breast cancer.

Almost patients received one chemotherapy (58.4%), whom received two agents (35.6%), three agents only 5%, and patients whom their regimen containing more than three agents only 1%. Examples of medications that may prescribed to the patients are anti-emetic agents,

anti-pyrectics, and analgesics, in addition to the patient usual drug to treat his chronic conditions.

In table 2, types of adverse effects that reported in pharmacovigilance center in each oncology center. Nausea and vomiting represent the higher incidence (40.6%). Nausea and vomiting are 2 serious and related side effects of cancer chemotherapy. These adverse effects can cause significant negative impacts on patients' quality of life and on their ability to comply with therapy. Also, nausea and vomiting can result in anorexia, decreased performance status, metabolic imbalance, wound dehiscence, esophageal tears, and nutritional deficiency. Drugs that cause nausea and vomiting (chemotherapy induced nausea and vomiting CINV) classified into four classes:

- *Highly emetogenic:* medications or doses that cause CINV in >90% of patients
- *Moderately emetogenic:* medications that induce CINV in 30% to 90% of patients
- *Low emetogenic:* medications that are associated with CINV rates of 10% to 30%
- *Minimally emetogenic:* medications that cause CINV in <10% of patients. (4)

The pathophysiology of nausea and vomiting are explained in Fig. 1 (5). By understanding the mechanism, the anti-emetic agents are used to control DINV.

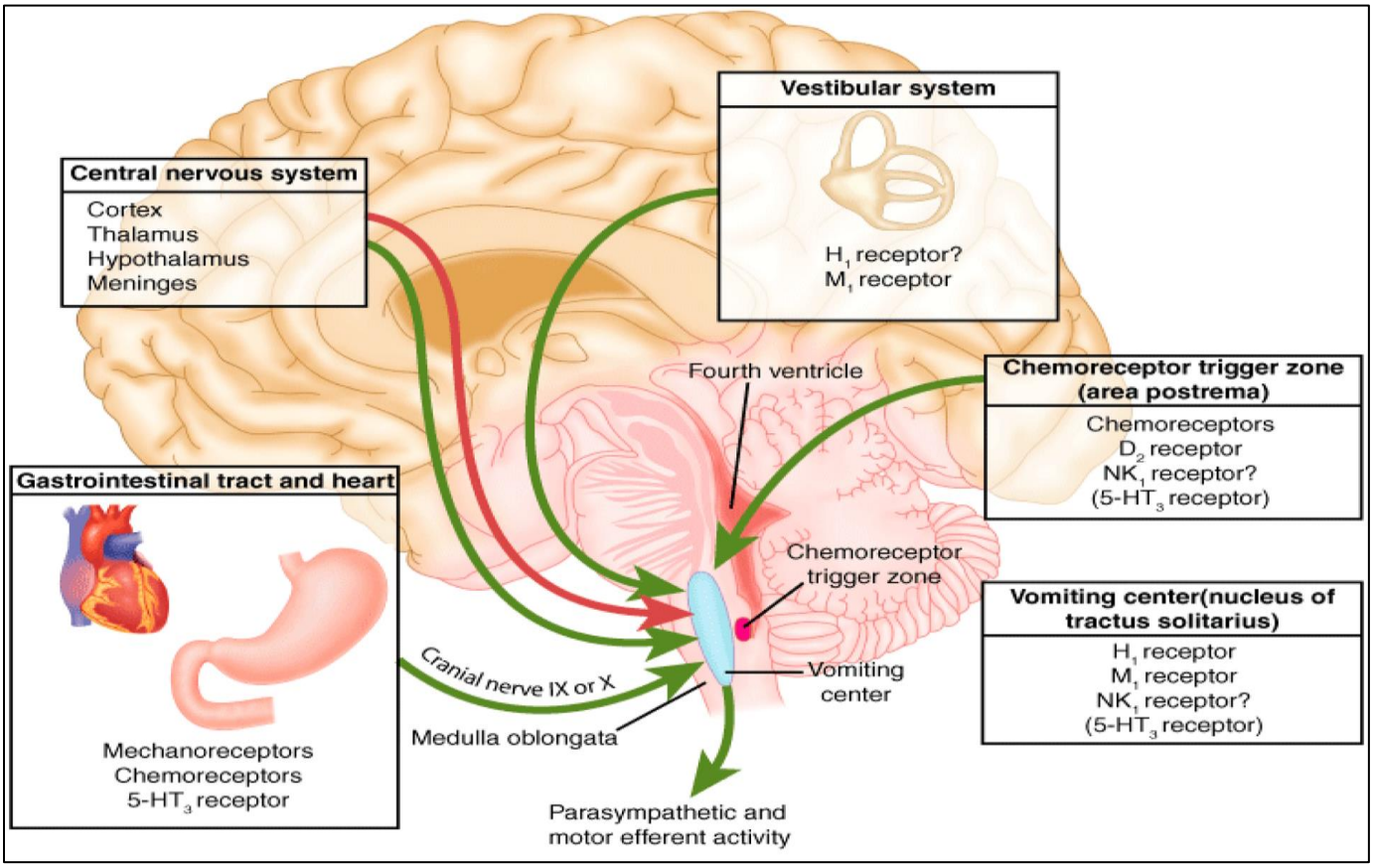


**Fig. 1. Pathways of Nausea and Vomiting in Patients Received Chemotherapy (5)**

Diarrhea, the second adverse effect of chemotherapy that recorded (11.9%) in recorded data. Diarrhea is a common side effect of chemotherapy, especially in patients suffering from advanced cancers. It is estimated that about 50%–80% of cancer patients suffer from chemotherapy-induced diarrhea (CID). CID is associated with a failure to retain fluid and electrolytes resulting in severe dehydration and electrolyte imbalances, malnutrition, or renal and cardiac dysfunction, all of which can lead to hospitalization and in severe cases, death.

The pathophysiology of CID is complex and involves multiple factors. It has been suggested that acute damage to the intestinal epithelium, including to the architecture of the crypts and villi, plays a significant role in disrupting the secretory and absorptive functions of the intestinal wall. Preclinical studies have shown that chemotherapeutics, induce significant apoptosis in intestinal crypt cells within the colon and jejunum. The need to compensate for the enhanced rate of apoptosis can result in metaplasia of goblet cells and increased production of immature secretory cells, thus contributing to the exacerbated mucus production associated with CID (6)

Fever is also reported in oncology centers, in percent 7.9%. Other studies mentioned chemotherapy cause fever and elevation body temperature, which can relate to infection that occurs during CT administration (infection resulted from patients low immunity due to CT) or may be related to drug induced fever, especially when bacterial culture is clear. The pathogenesis of drug fever related to CT other presence of infection has yet to be fully understood. It has been shown previously that proinflammatory cytokines such as tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), and interferon-g (IFN-g) are released during the administration of high doses of ARA-C and probably mediate the reaction, being known to act as endogenous pyrogens (7)

Bone pain, is another adverse effect reported by the oncology-pharmacovigilance center in Basra city, by percent of 8.9%. this adverse reaction resulted from progressive bone density loss and osteoporosis, enhancing muscle cramps, inducing trabecular bone loss, enhance muscle atrophy, and such changes will cause bone and muscle pain that range from mild to severs depending on degree of damage (8)

Hemorrhagic cystitis is defined as a diffuse inflammatory condition of the urinary bladder due to an infectious or noninfectious etiology resulting in bleeding from the bladder mucosa. A wide variety of agents including chemotherapeutic drugs are implicated in the

development of hemorrhagic cystitis, like ifosfamide and cyclophosfamide . such adverse effect can control or managed by reducing the dose, if applicable, or by increase hydration to improve urination and aiding preserve kidney function (9)

Chemotherapy-induced thrombocytopenia (CIT) is a common complication of the treatment of non-hematologic malignancies. Many patient-related variables (e.g., age, tumor type, number of prior chemotherapy cycles, amount of bone marrow tumor involvement) determine the extent of CIT. CIT is related to the type and dose of chemotherapy, with regimens containing gemcitabine, platinum, or temozolomide producing it most commonly. Thrombocytopenia creates a number of problems in the care of the cancer patient. At platelet counts less than $10x10^9$/L, spontaneous bleeding may be increased. At platelet counts less than $50x10^9$/L, surgical procedures are often complicated by bleeding. At platelet counts under $100x10^9$/L, chemotherapy and radiation therapy may be administered with caution thereby decreasing dose intensity and clinical outcome.[1] Therapeutic and prophylactic platelet transfusions create the additional risk of infusion-related complications and might be immuno-suppressive (10)

Modern cancer therapy is based on complex treatments involving combinations of chemotherapeutic agents, biologic agents, and endocrine agents, Furthermore, caregivers often add palliative and analgesic therapies, antiemetics and non-pharmaceutical complementary and alternative medicines to help manage ADRs. These complex combinations may increase the number of interactions among drugs or between drugs and other products, including natural ones. So, it is necessary to record and follow-up any complication or drug reaction can result, which is the main role of pharmacovigilance center. The importance of pharmacovigilance in oncology must be highlighted with every effort, to improve safety and offer cancer patients every possible help to improve their quality of life during such a critical period of their lives. (11)

At the appendix part, examples on adverse drug reactions reported by pharmacovigilance centers (11)

## Conclusion:

Pharmacovigilance centers in hospitals are very important in recording the usual and unusual adverse drug reaction that may be happened during drug administration, which will help to control any type of adverse drug reaction, give alarm about serious one, help to stop rout or drug administration if it reported very severe or lethal. As a net result, this is helpful method to save patient life and improve its quality.

## Limitation:

Duration of reported data is for one year, which if it is longer, can report more and miscellaneous data. Method of treating ADR is not reported in this study.


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## Appendix:

**Table 2** Adverse effects caused by systemic antineoplastic treatments, and their prevention and management

| Adverse effect | Causative agent | Prevention | Management |
|---|---|---|---|
| Cardiovascular toxicity | Anthracyclines, alkylating agents, taxanes, targeted therapies, monoclonal antibodies | Basal assessment of cardiac function (ECHO, LVEF, ECG); evaluation of cardiovascular risk factors and comorbidities | Withdrawal of cardiotoxic therapy; treatment of cardiac dysfunction; ACE inhibitors or beta-blockers should be considered [10] |
| Cognitive dysfunctionality (chemo-brain, chemo-fog) | Potentially all | Ask patients to report any mental disturbances | No recommendations available |
| CVC-related complications (infections, thrombosis, extravasation) | All drugs administered in intravenous infusions through CVCs | Monitor patients for CVC-related infections; control regular venous flux and functioning of infusion disposables; train health care personnel | Suspension of intravenous infusions; early surgical procedures to manage extravasation; surgical removal of CVCs; antidotes specific to drugs in extravasation |
| Dermatological toxicity (skin, hair and nail modifications) | Potentially all systemic cytotoxic treatments (targeted therapies included) | Risk assessment; patient education. Previous treatments can result in cumulative toxicity | Symptomatic treatment based on the grade, type of therapy, and type of cutaneous reactions |
| Diarrhea or constipation | Antimetabolites, topoisomerase inhibitors, vinca alkaloids, targeted therapies | For diarrhea: fluid intake to prevent dehydration, dietary modifications, nutritional support. For constipation: dietary modifications, fluid intake, physical activity | For diarrhea: antidiarrheal drugs (loperamide), somatostatin analogs if appropriate, probiotics, sulfasalazine. For constipation: laxatives (osmotic or stimulant), opioid antagonists (e.g. methylnaltrexone) for opioid-induced constipation |
| Fatigue | Microtubule agents | Consider concomitant factors (e.g. pain, anxiety) | Suggest behavioral modifications; provide nutritional, physical and psychological support; consider pharmacological and non-pharmacological approaches |
| Febrile neutropenia | Taxanes, anthracyclines, antimetabolites, topoisomerase inhibitors, immunomodulatory drugs | Assess the patient's risk (MASCC score). Use of antibacterial prophylaxis is usually contraindicated. Prophylaxis with G-CSF is recommended if risk is > 20% or if the patient is elderly or has comorbidities | Follow international guidelines (ASCO-ESMO). Patient education and local hospital policies are fundamental |
| Hormonal impairment, infertility | Cyclophosphamide, taxanes, irinotecan, platinum derivatives | Offer procedures to preserve fertility (e.g. sperm or oocyte banking, shield protection during radiotherapy, ovarian transposition); consider using LH-RH agonists as protection (in women) during chemotherapy | Consider using hormonal replacement therapy and pharmacologic treatment to correct male sexual dysfunction |
| Infections | Immunomodulatory agents, transplantation | Follow international guidelines (ASCO-ESMO) for prophylaxis (bacterial-viral-fungal); use prophylactic drugs (antibacterials or antivirals) correctly to avoid drug resistance | Accurate diagnosis is essential for choosing a treatment. Anti-infective drugs should be administered to the site of infection (e.g. respiratory tract, head-neck, gastrointestinal, skin, CVC) |
| Infusion reactions | Potentially all | Risk assessment (e.g. medical history, allergic disorders); premedication with corticoster- | Stop or slow the infusion rate, symptomatic treatment |

**Table 2** (continued)

| Adverse effect | Causative agent | Prevention | Management |
|---|---|---|---|
| Mucositis | Antimetabolites, methotrexate, cyclophosphamide, platinum derivatives, targeted therapies, taxanes, vinorelbine, 5-fluorouracil | Risk assessment; preventive measures (e.g. oral care, regular dental examinations), nutritional support | Suggest behavioral modifications (avoid alcohol, tobacco, hot foods). Patient education by mean of local hospital guidelines is essential. Use apposite oral solutions to manage symptoms and prevent oral infections [11] |
| Nausea and vomiting | Anthracyclines and cyclophosphamide in combination, platinum derivatives, azacitidine, bendamustine, ifosfamide, irinotecan, trabectedine | In case of chemotherapy of high emetic risk, give a single dose of $5HT_3$ receptor antagonist, dexamethasone and $NK_1$ receptor antagonist before chemotherapy to prevent acute nausea and vomiting | Follow international (ASCO-ESMO-MASCC) and evidence-based guidelines. Antiemetic drugs (corticosteroids, 5-$HT_3$ and $NK_1$ receptor antagonists, dopamine antagonists, benzodiazepines) must be used in accordance with the emetogenic potential of drugs in the chemotherapy regimen [12] |
| Neuropathic pain | Microtubule agents (taxanes, vinca alkaloids, eribulin), platinum derivatives | Monitor first infusion, premedicate (corticosteroids or antihistamines), and identify high-risk patients. Previous treatments can lead to cumulative toxicity | Stop infusion of chemotherapy; give nonopioids, at discretion, with or without strong opioids, amitriptyline 25–75 mg/day or gabapentin 300–3600 mg/day [13] |
| Palmar-plantar erythrodysesthesia (hand-foot skin reaction) | Anthracyclines, antimetabolites, immunomodulatory therapies and targeted therapies | Monitor the patient's symptoms and behavioral modifications: avoid skin, hand and feet pressure, sun exposure, hot water, friction | Administer oral pyridoxine (up to 150 mg/day); use skin creams (keratolytics or emollients); discontinue or temporarily suspend therapy |
| Thrombosis | Surgical procedures, non-surgical anticancer treatments | For surgical procedures and implanted accesses, prophylaxis includes low molecular weight heparin, fondaparinux, warfarin | Anticoagulant therapy, low molecular weight heparin, fondaparinux. The use of new anticoagulants in oncology is still under evaluation and is recommended only in select cases |

*ASCO-ESMO* American Society of Clinical Oncology-European Society for Medical Oncology, *CVC* central venous catheter, *ECHO* echocardiography, *LVEF* left ventricular ejection fraction, *ECG* electrocardiography, *MASCC* Multinational Association of Supportive Care in Cancer, *G-CSF* granulocyte-colony stimulating factor, *5-$HT_3$* serotonin$_3$, *$NK_1$* neurokinin$_1$