Seminars in Oncology Nursing 40 (2024) 151553

Contents lists available at ScienceDirect

Seminars in Oncology Nursing

journal homepage: https://www.journals.elsevier.com/seminars-in-oncology-nursing

Early Recognition and Management of Side Effects Related to Systemic Anticancer Therapy for Advanced Breast Cancer

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ARTICLE INFO

Key Words:
Advanced breast cancer
Management of side effects
Oncological emergencies
Supportive care
Treatment-related side effects

ABSTRACT

Objectives: Advances in science and technology have meant there are numerous treatment options available for people with advanced breast cancer (ABC). However, each therapeutic approach can cause side effects or adverse events, which can significantly affect the person's quality of life, overall well-being, and, in some instances, safety. This report presents an overview of the common side effects of systemic anticancer therapy and ways to manage them.
Data Sources: Data sources include peer-reviewed articles sourced in electronic databases and national and international best practice guidelines (ESMO, ASCO, and MASCC guidelines).
Conclusion: Systemic anticancer therapies have side effects that healthcare professionals need to know about to monitor and manage them in early stages. Nurses play an important role in patient education, early identification, monitoring, and management of treatment side effects.
Implications for Nursing Practice: People with ABC face many challenges during their treatment journey. Oncology nurses, specialist nurses, and nurse practitioners can be of support by providing preventive measures and side effects management at an early stage. Nurses need to have a good understanding of toxicity management but also advanced tumor-specific cancer knowledge of the different subtypes of ABC and holistic assessment skills. They are also key to providing support and enhancing self-management and early recognition of side effects.

Introduction

People with advanced breast cancer (ABC) are living longer.[1] Advances in science and technology have meant there are numerous treatment options available for people with ABC. While ABC is not curable, the aim of treatment is to maintain the person's health-related quality of life (HR-QOL),[2] control symptoms, delay progression, and prolong overall survival.[3] Treatment approaches are varied and include endocrine therapy, chemotherapy, targeted therapy, immunotherapy, and antibody-drug conjugates as well as radiotherapy. This report will focus on the common side effects of systemic anticancer treatments (SACTs) and ways to manage them.

Though treatment options are varied, each treatment has potential side effects and the ability to cause adverse events (AEs). *Side effect* and *adverse event* are terms often used to define the same thing, but their definitions differ. According to the Common Terminology Criteria for Adverse Events (CTCAE) (cancer.gov),[4] an adverse event is "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure," while side effects are expected but undesired effects of the treatment that can occur and are associated with the medical treatment; we will explore them in this article.

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https://doi.org/10.1016/j.soncn.2023.151553

TABLE 1
Common Terminology Criteria for Adverse Events (CTCAE).[4]

Grade 1: Mild	Clinical or diagnostic observations only; intervention not indicated
Asymptomatic or mild symptoms	Nursing support and advice would be provided
Grade 2: Moderate	Need medical intervention but do not need to be admitted to hospital
Limiting instrumental activities of daily living	Minimal, local, or noninvasive intervention indicated
Grade 3: Severe or medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated
Limiting self-care activities of daily living	
Grade 4: Urgent	Needs urgent intervention; otherwise they may reach grade 5
Life-threatening consequences	
Grade 5: Death related to the adverse event	

Inadequate management of treatment toxicities can severely affect a person's quality of life and lead to increased morbidity and mortality. Comprehensive assessment of side effects is essential to identify risk and manage toxicities early. When assessing specific toxicities associated with cancer treatments, a useful resource is the CTCAE.[4] CTCAE Version 5 (2017) is currently used, though version 6 is due to be published imminently.

The CTCAE is widely accepted as the standard classification and severity grading scale for side effects in cancer therapy, clinical trials, and other oncology settings. Within the criteria, there is a description of the side effect and grading to assess the severity, from grade 1 (mild) through to grade 5 (life threatening) (Table 1). Side effects may be assessed in a three-part scale that may measure (1) if a side effect is developed (appearance symptoms and signs), (2) the intensity/severity of the side effect (grading), and (3) if the patient is distressed/suffers from it (impact on HR-QOL).

There are clinician-graded and self-reported versions of CTCAE. Grading of the severity and impact of side effects by the patients themselves may improve diagnosis and management of these specific reactions and gives a better understanding of the effects on HR-QOL.[5,6]

Nurses play an important role in patient education, early identification, monitoring, and management of treatment side effects.[7] In some countries, such as England, Canada, and the United States, it is now common practice for a specialist nurse to call patients in the first days of starting a new treatment.[8,9] Within nursing practice, the United Kingdom Oncology Nursing Society (UKONS) Triage Tool[10] is known and recognized as a useful triage tool that has been translated into other languages. The UKONS tool gives a description of the symptom and a grade from 0 (no change, normal) to 4 (life threatening, very severe). It gives exact descriptors in the grades; for example, number of times the person has diarrhea in 24 hours. It also gives management advice, such as "Drink more fluids, obtain stool sample, commence regimen specific antidiarrheal." The grade and descriptor are color coded from green (providing support and advice) to red (needing urgent treatment). While CTCAE is a medical tool to grade AEs, the UKONS tool offers the nurses an instrument that quickly identifies patients at high risk of harm, allowing rapid assessment or intervention that is nursing advice based.

There are other tools to assess side effects. For example, Franzoi et al[11] developed an algorithm of workflow to assess the side effects of endocrine therapy, which may be a useful approach for assessing and managing side effects of any treatment for people with ABC (Fig 1).

Side Effects of Endocrine Therapies

People with hormone receptor (HR)-positive, *HER2*-negative ABC will be given endocrine therapy. Tamoxifen, a selective estrogen receptor modulator; aromatase inhibitors such as anastrozole, letrozole or exemestane; or fulvestrant, a selective estrogen receptor down-regulator, are the most common drugs used. Side effects of endocrine therapies include hot flashes, weight gain, musculoskeletal symptoms, fatigue, and sexual dysfunction. Franzoi et al[11] reviewed evidence-based approaches to manage side effects of endocrine therapy for people with breast cancer. Fig 2 shows the interventions associated with each side effect and their relative efficacy (color coded). They include pharmacological as well as nonpharmacological and complementary therapy interventions. For example, for fatigue, physical therapy and cognitive-behavioral therapy are the interventions that have shown efficacy in randomized controlled trials.[11] While some of the interventions are known to be used in other therapies and cancer, this study evaluated only interventions with people on hormone therapies for breast cancer.

Side Effects of Targeted Therapies

The development of targeted therapies has changed the landscape of treatment for people with ABC. Types of targeted therapies include monoclonal antibodies (eg, trastuzumab for *HER2*-positive breast cancer), kinase inhibitors (CDK4/6 inhibitors for HR-positive breast cancer), mTOR inhibitors (for HR-positive breast cancer), and P13K inhibitors and PARP inhibitors (for *BRCA*-positive breast cancer).[12] Although targeted therapy limits damage to healthy cells, it can still have side effects.[12] These vary for each person depending on the drug given and how the body responds. Skin reactions and GI side effects are the most common side effects. Skin reactions may include sensitivity to sunlight, skin redness, swelling, and dry, flaky skin; a rash that looks like acne or pimples on the face, scalp, or upper body (acneiform rash); and a skin reaction on the palms and soles causing tenderness and blisters.

Skin reactions from targeted therapy may be more severe or last longer than skin problems from chemotherapy.[12-14] There are a number of excellent reviews concerning treatment and management.[12-15] They all have in common the importance of skin care to minimize side effects. For example, pruritus can often be avoided by using creams with urea and avoiding ultraviolet radiation (UV) and excessive washing. As sensitivity to sunlight is common with targeted treatments, UV protection is always recommended. If skin reactions affect a person's daily life, they are usually managed with steroids. Most side effects are reversible, but it is of utmost importance to keep the skin in a healthy condition.[17] It may be that treatment needs to be stopped or adjusted to minimize side effects.[15]

The most common gastrointestinal reaction is diarrhea. Guidelines for the assessment and management of diarrhea include grading of severity of symptoms. Table 2 shows the current management guidelines.

- Grade 1 is an increase of up to four stools per day over baseline.
- Grade 2 is an increase of four to six stools per day over baseline.
- Grade 3 is an increase of more than seven stools per day and interfering with daily living.
- Grade 4 is life-threatening consequences such as hemodynamic collapse[16]

Targeted therapies may cause nausea and vomiting (normally managed with antiemetics) but may also cause constipation. While gastrointestinal side effects are similar to those of chemotherapy,

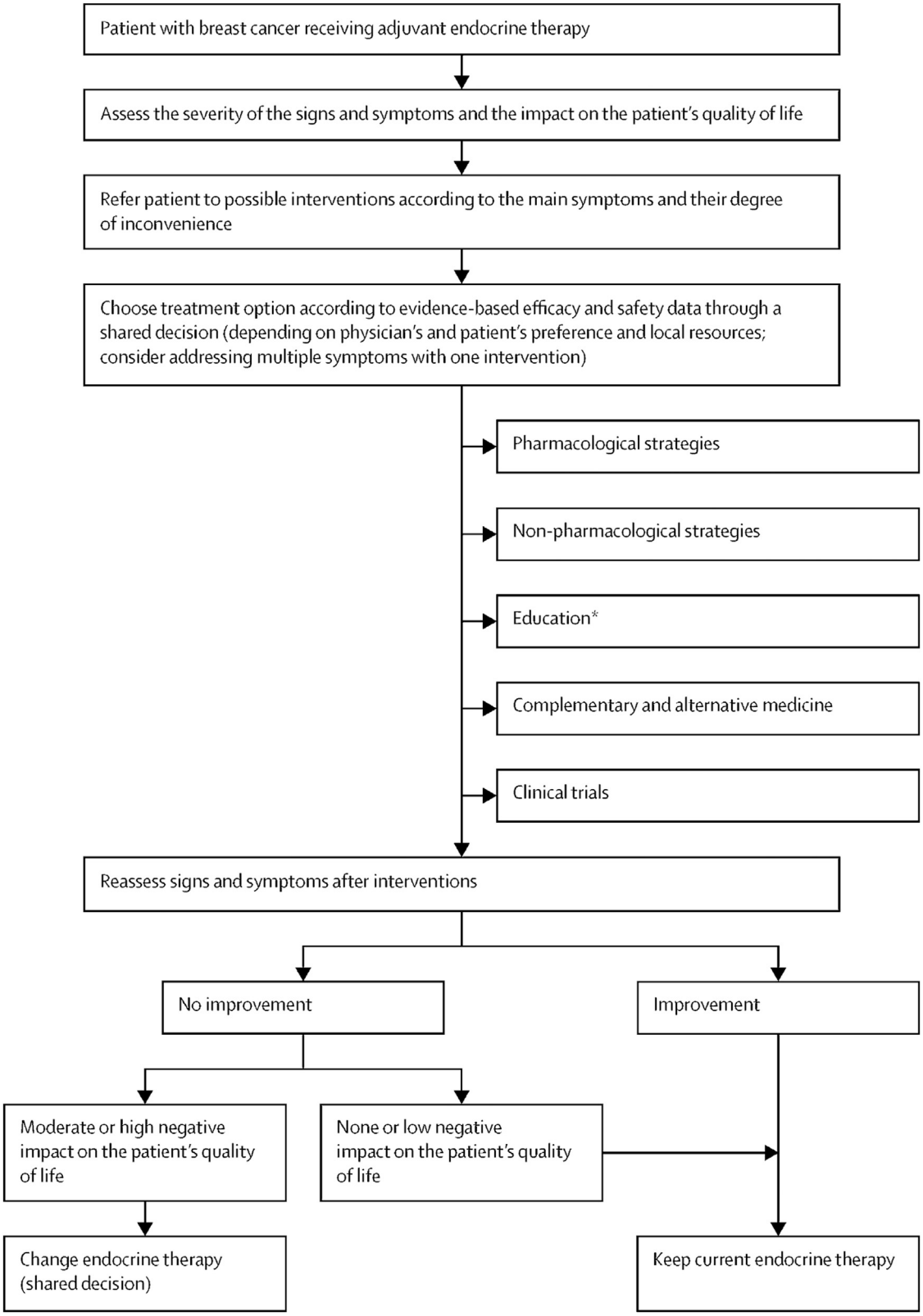

Fig 1. Workflow to assess side effects of endocrine therapy. (From Franzoi et al.[11])

management of the side effects of targeted therapy often needs a different approach from other cancer treatments.[12]

There are other side effects known from targeted therapies that include fatigue, rash, loss of appetite, hair loss, low red blood cell counts, and abdominal pain. Serious side effects can include neutropenia (with an increased risk of infection and sepsis) and infusion reactions (similar to an allergic reaction) when the drug is infused.[16] Steroids are normally given before each treatment to lower the

Fig 2. Interventions for side effects of endocrine therapy. (From Franzoi et al.[11])

chances of infusion reactions. People are given advice concerning infections.

More serious side effects include cardiac dysfunction, interstitial lung disease, and liver problems. The incidence of cardiac dysfunction related to trastuzumab in people with ABC ranges from 3% to 7% and increases to 11–18% when combined with chemotherapy.[18] These effects are normally monitored from baseline to identify them as early as possible, but they are difficult to manage. Also, symptoms can be very vague, for example, a cough in lung or cardiac toxicities.[12] Cardiac function should be assessed prior to treatment, at 3-month intervals, and if patients complain of cardiac symptoms as per European Society of Medical Oncology (ESMO) Clinical Practice Guidelines.[19] Due to the potential risk of interstitial lung disease and liver disease, respiratory and liver functions are both also monitored regularly. When these side effects appear, the management normally includes cessation or dose reduction of the targeted therapy and steroids.[13] See Fig 3 for all side effects from targeted therapies. They are color coded depending on how frequent they are (green frequent, yellow less frequent but important, red when despite not being frequent are important as can lead to life-threatening or -limiting side effects).

Side Effects of Immunotherapy

Cancer immunotherapy has also had a great impact on the treatment of ABC, especially, but not only, of triple-negative breast cancer when there is a protein expression in the cancer cells.[20] Programmed cell death ligand 1 (PD-L1) is a protein that stops the immune system from attacking healthy cells in the body. When found on the surface of cancer cells, PD-L1 interacts with receptors on the T cell to disable the body's immune system, affecting the ability of the body to destroy

TABLE 2
Guidelines for Management of Treatment-Induced Diarrhea.[17]

Uncomplicated Grade 1–2	• Stop lactose-containing products • Drink 8–10 large glasses of clear liquids • Eat frequent small meals
Grade 2	• Hold cytotoxic chemotherapy and consider lapatinib dose reduction • Administer standard dose loperamide: initial dose 4 mg followed by 2 mg every 4 hours • Consider administration of loperamide until diarrhea free for 12 hours
Grade 3–4 or grade 1 or 2 with complicating features	• Consider hospital admission • Administer octreotide • Use IV fluids as appropriate • Use prophylactic antibiotics, especially if diarrhea is persistent beyond 24 hours or there is fever or grade 3–4 neutropenia • Hold cytotoxic therapy and lapatinib

cancer cells.[21] Programmed cell death protein 1 (PD-1) is an inhibitory receptor that is expressed by all T cells during activation.[20]

The principal method for inhibiting the PD-1 pathway clinically has been through the development of genetically engineered monoclonal antibodies, such as pembrolizumab, that inhibit either PD-1 or PD-L1 function.[20]

Immunotherapy side effects usually occur within weeks to 3 months after initiation of immunotherapy. However, they may occur up to 1 year after discontinuing treatment.

The most common side effects from immunotherapy are skin reactions, diarrhea, and endocrinopathies.[21] Skin reactions normally are not severe and can include rashes, blisters, or erythema. Other side effects associated with immunotherapy treatment may include but are not limited to chills, constipation, coughing, decreased appetite, diarrhea, fatigue, fever and flu-like symptoms, headache, infusion-related reaction or injection site pain, and itching. The available evidence suggests that the majority of immunotherapy side effects are manageable with the use of steroids and other immune-modulating drugs.[21,22]

Although short- to medium-term toxicity across most organ systems appears manageable and is mostly reversible, there are some side effects that may have permanent consequences, including diabetes. Endocrinopathies often need long-term management, such as hypothyroidism, that can occur in around 6% of patients treated with anti–PD-1.[21] See Fig 4 for side effects from immunotherapy, color coded depending on how frequent they are.

The ESMO Practice Guidelines[21] advocate that peoples' susceptibility to immunotherapy side effects should be assessed and patients should be informed of the potential side effects, ensuring they report directly to the treating physician or team. Workup should include history, general physical condition, autoimmune diseases, baseline laboratory tests, and radiological scans. If the person has current or previous autoimmune disease, there is risk of worsening their

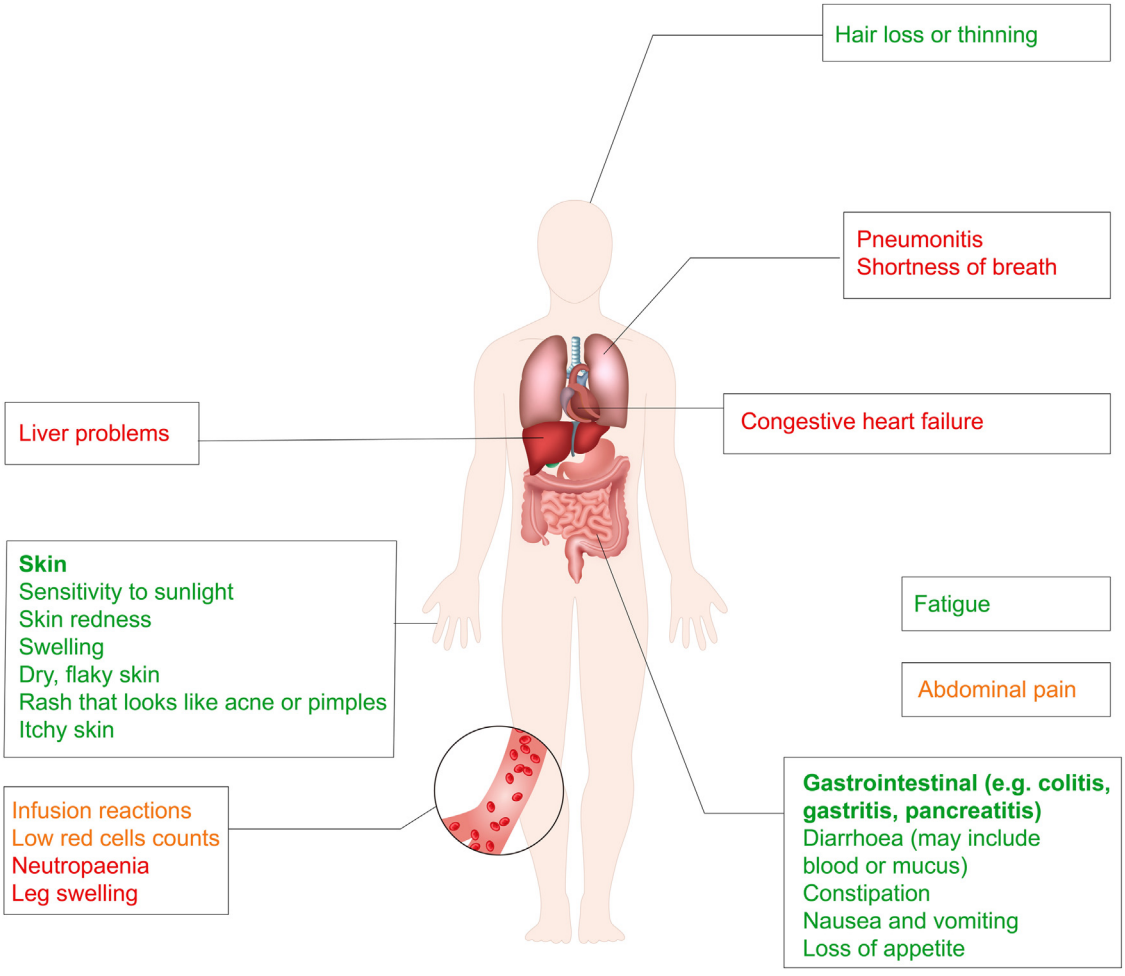

Fig 3. Side effects of targeted therapies.

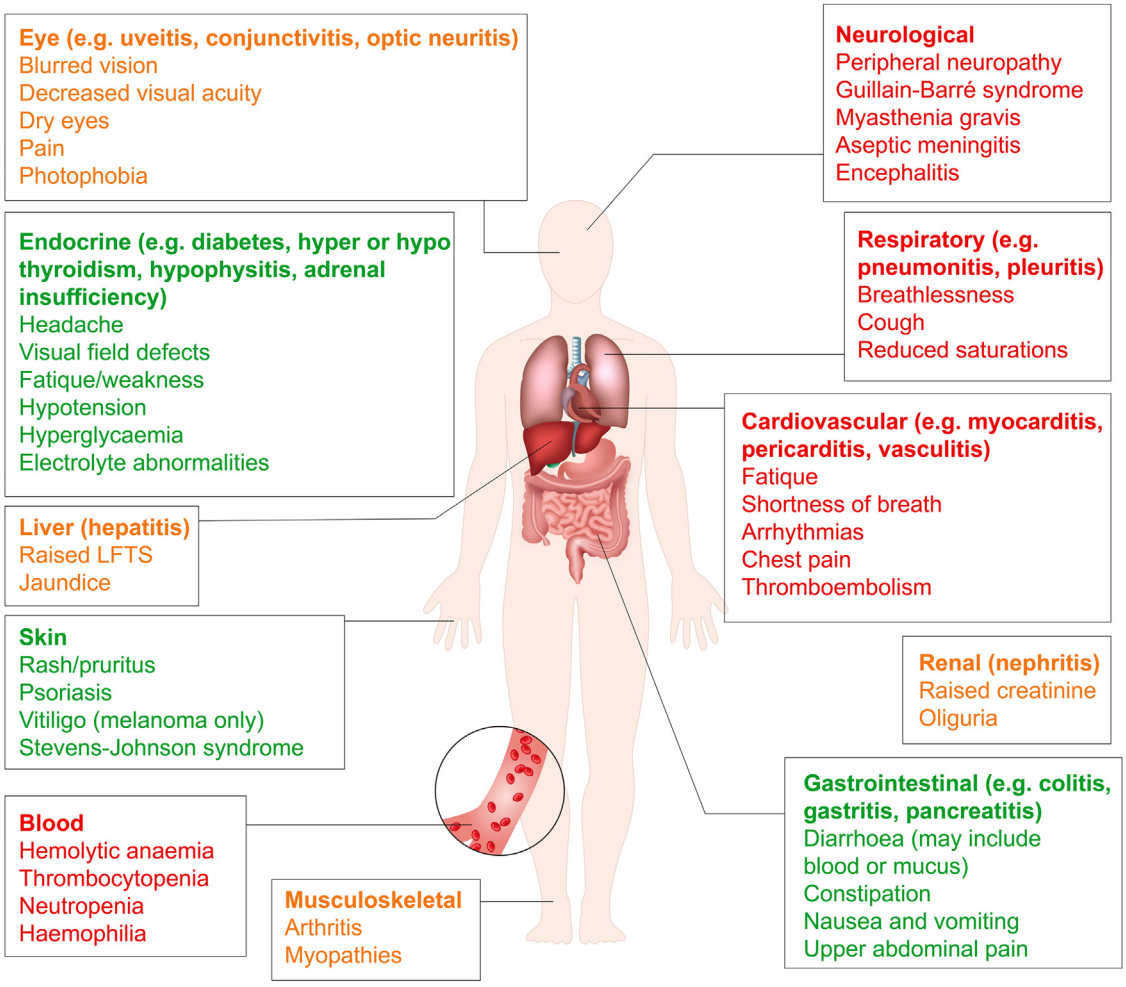

Fig 4. Side effects of immunotherapies.

autoimmune disease while on immunotherapy treatment. If they have had previous ipilimumab-related side effects, there is a risk of developing side effects following anti–PD-1 treatment, and vice versa. Once side effects have developed, prompt workup and action are required and referral to other specialists should be considered such as endocrinologists. Steroids and immunosuppressive agents are commonly used in immunotherapy side effects. If side effects are minor, patients are advised to take oral medications and are monitored at home. For example, grade 1 diarrhea can be treated with loperamide, and some skin reactions can be treated with topical cream. As with targeted therapies, cardiac function, lung health, and blood tests are regularly assessed to mitigate the risk of complications. Patients are advised to report their symptoms as, in many cases, they can be vague such as fatigue or weakness. Full information and advice for management is given within the ESMO Clinical Practice Guidelines for Management of toxicities from immunotherapy.[21]

Side Effects of Chemotherapy

For people with ABC, chemotherapy is often given in combination with immunotherapy or targeted therapy, or it is given when a rapid response is needed as in the case of extensive visceral disease (where excessive tumor burden is leading to severe organ dysfunction with poor prognosis).

Common short-term side effects include hair loss, fatigue, loss of appetite, nausea and vomiting, constipation or diarrhea, mouth sores, skin and nail changes, and neutropenia.

Assessment and management of chemotherapy side effects have been written about extensively in the literature, such as Roe and Lennan.[23] For the most part, short-term side effects are better managed as prevention.[23] For example, medication to prevent nausea and vomiting are given as standard treatment, and scalp cooling can prevent partly or entire hair loss with some kind of chemotherapies. Healthcare professionals give people advice about living well when having chemotherapy, ensuring they eat and drink well, do exercise, and maintain good mouth hygiene. Fatigue and loss of appetite are quite common in people with ABC with or without chemotherapy and can be worse when having chemotherapy. There is evidence suggesting that exercise can improve fatigue.[24,25] People are recommended to eat small meals or snacks several times a day if they cannot eat normal meals due to nausea or lack of appetite. People should also receive advice about being extra cautious at the nadir in chemotherapy (7–12 days). See Fig 5 for the most common and important side effects from chemotherapy color coded depending on their frequency.

Implications for Nursing Practice

Each section within this article highlights (1) the importance of healthcare professionals and patients being able to swiftly recognize symptoms as attributable to drugs. (2) undertaking accurate assessments using validated criteria, allowing the precise impact of the side effect on quality of life encompassing assessment of a patient's personal physical and psychological functionality, and (3) provide

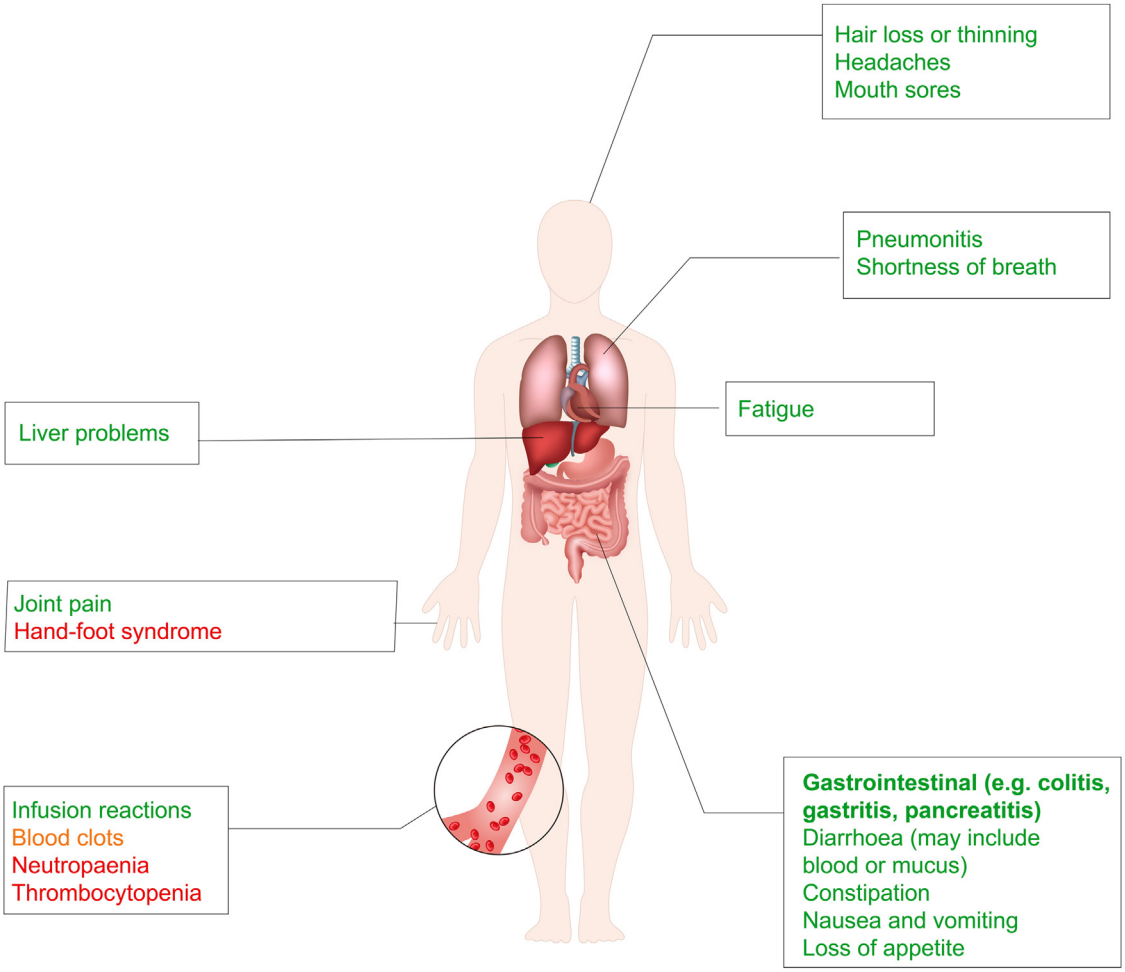

Fig 5. Common side effects of chemotherapies.

evidence-based advice/interventions using tools such as UKONS initial management guidelines or refer on to a specialist medical practitioner/nurse specialist.

When giving information about new treatments, it is important for healthcare professionals to explain the side effects and potential risks to patients and their support system (family, carers) from the beginning of treatment. Patients need to know when it is important to seek advice and help.

Nurses have a crucial role in monitoring, assessing, escalating, and supporting in the coordination of treatment of the side effects.[26] The importance of maintaining the right balance between ABC disease control with drug continuation at the optimum tolerable doses, versus SACT dose modifications, deferrals, and, in some cases, omission, are vital aspects of nursing practice.

Management and decision-making related to treatment side effects requires holistic assessment skills, a good understanding of toxicity grading, and up-to-date knowledge of interventions to alleviate side effects. Knowledge of the different subtypes of ABC allows a better understanding of which treatments are used depending on the subtypes.

Both on or off treatment, nurses predominantly have most contact with patients with ABC and their families, and it is through their therapeutic relationships, continuity of care, and truly knowing the person and their family impact on quality of life is easily interpretable. The breast care (or specialist) nurse makes a real difference in helping people navigate living with ABC and play an important role in their treatment.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Celia Diez de los Rios and Theresa Wiseman were Guest Editors for the Metastatic Breast Cancer Special Issue of Seminars in Oncology Nursing. As an author of this article, they did not participate in any editorial process or decision-making, which was handled by another editor.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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