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Chemotherapy in patients with early breast cancer: clinical overview and management of long-term side effects

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ABSTRACT

Introduction: Neo/adjuvant therapy for early-stage breast cancer has become increasingly common in the last few decades; as a consequence, the number of breast cancer survivors experiencing often debilitating long-term side effects has increased, and thus the need for a comprehensive approach to the variety of symptoms involved.

Areas covered and methods: We performed a literature search on the main public scientific databases (PubMed, Embase, Cochrane, and CrossRef) from 2000 to April 2022 to identify prevention and management strategies for the most common long-term side effects, including fatigue, insomnia, peripheral neuropathy, cognitive impairment, estrogen deprivation, cardiotoxicity, and second cancers.

Expert opinion: Long-term toxicities may affect a majority of breast cancer survivors, significantly interfering with their quality of life. Although there are guidelines for the management of isolated side effects, such as peripheral neuropathy, we aim to provide a more inclusive clinical-oriented approach, focusing on both prevention and therapeutic strategies

1. Introduction

Breast cancer (BC) is the most common type of cancer in women worldwide; through the last two decades, the use of (neo)adjuvant therapies in early stage became state of the art and played a relevant role in improving survival rates [1]. Thus, the ever-increasing number of breast cancer survivors experience unique long-term physical, psychological, and psychosocial changes, which can strongly affect their quality of life (Figure 1.) [2] Given the dearth of evidence regarding prevention or treatment of long-term side effects, there is an urgent need for the identification and development of useful strategies to manage this vast array of debilitating symptoms. Herein, we provide a comprehensive review of management strategies for the most common long-term chemotherapy toxicities experienced by breast cancer survivors; these are summarized in Table 1.

2. Methods

We performed a literature search on the main public scientific databases (PubMed, Cochrane, Embase, and CrossRef), for manuscripts published from 2000 to April 2022, using combinations of the following keywords: 'early breast cancer,' '(neo) adjuvant chemotherapy,' 'fatigue,' 'insomnia,' "neurotoxicity" "CIPN" "peripheral neuropathy", "cognitive impairment," "chemobrain," "fertility," "bone health," "menopause," "menopausal symptoms," "cardiac toxicity", and "second cancer." Furthermore, we identified additional data checking the

references of other relevant reviews, guidelines, and published papers in this field, and through experts' advice.

3. Fatigue

Cancer-related fatigue (CRF) is defined as 'a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness, related to cancer or cancer treatment, that is not proportional to recent activity and interferes with usual functioning' [3]. Fatigue is the most common side effect experienced by BC survivors; its incidence can reach 50% of patients and persist for at least 5 years after completion of treatment. These patients usually show worse scores for all quality of life (QoL) functions [4].

Adjuvant chemotherapy (alone or in association with radiotherapy) is associated with a higher risk of developing CRF [4,5]; while use of taxanes increases fatigue while on treatment [6], it does not seem to influence neither prevalence nor severity of long-term fatigue [5]. Endocrine treatment, which is often given after chemotherapy in early breast cancer patients, can also contribute to the severity of this symptom.

3.1. Management

3.1.1. Screening and prevention

Cancer patients should be screened and assessed during and after chemotherapy treatment to enable timely management strategies. Fatigue can be self-reported by a Numeric Rating Scale (NRS) tool [7], although in clinical practice, it is often

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ranked by physicians according to the Common Terminology Criteria for Adverse Events (CTCAE) scale. Several multidimensional tools have been validated, but there is currently no clear evidence about the most appropriate one [8]. Recently, a predictive tool for long-term severe fatigue was validated based on the results of the CANTO trial [9]; in this trial, the authors identified clinic-behavioral risk factors and generated a risk model for severe fatigue 2 years after diagnosis of breast cancer. Pretreatment fatigue, younger age, and symptoms at the time of diagnosis (such as pain, insomnia, depression, and anxiety) represented the most relevant predictors of long-term fatigue.
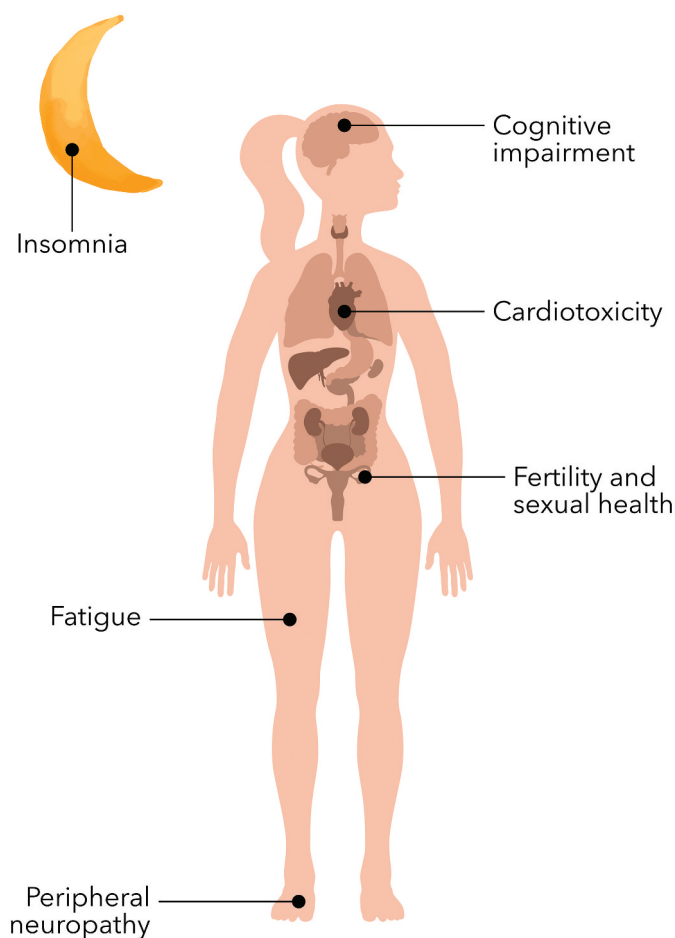

Figure 1. Long-term side effects of chemotherapy for early breast cancer.

There is no evidence about the role of prevention strategies in this setting. Patients who report a high score in the aforementioned tools should be investigated for concomitant physical causes requiring treatment (such as anemia; active infection; malnutrition; and thyroid, renal, cardiovascular, and pulmonary disease) [10–12]; moreover, a psychological evaluation to identify an underlying depressive disorder should be performed.

A recent study from Antonuzzo et al. demonstrated that providing information leaflets, associated to a phone-based nurse monitoring assessment and intervention, significantly reduced the time spent with both grade ≥3 fatigue (14.5% vs. 17.2%, $p = 0.015$) and grade ½ fatigue (60.3% vs 63.3%, $p \leq 0.05$) [13].

3.1.2. Non-pharmacological interventions
Although there is a plethora of data regarding the benefits of moderate intensity exercise in cancer patients, there is no specific exercise prescription for cancer-related fatigue. Two different meta-analyses concluded that moderate-intensity exercise, combining aerobic with strength and resistance training, reduced fatigue both during and after cancer therapy [14,15]. Walking at a moderate intensity has also been proven to reduce fatigue, sleep disruption and depression [16]. ASCO guidelines on exercise report significant improvements in fatigue as a result of aerobic and combined resistance and aerobic exercise interventions [17].

Psychoeducation interventions and cognitive behavior therapy have been proven clinically effective in reducing fatigue in cancer survivors [18]. Some evidence suggests that mindfulness-based stress reduction (MBSR), a combined treatment of meditation exercises and psychoeducational elements, cognitive-behavioral interventions, and movement exercises may be useful in this setting [19].

In two systematic reviews, yoga was found to be effective in decreasing CRF [20,21].

3.1.3. Complementary medicine
No nutraceutical intervention has shown efficacy in the management of CRF in breast cancer survivors. A double-blind, randomized, placebo-controlled phase 3 trial showed a benefit for use of Wisconsin ginseng on a heterogeneous population with different neoplasms and different stages of disease [22]. There are conflicting data regarding use of guarana, while a placebo-controlled trial of mistletoe in BC patients undergoing treatment with CMF (cyclophosphamide, methotrexate, fluorouracil) showed an improvement in fatigue while on chemotherapy; however, there is no reported long-term outcome [23]. Acupuncture appears to be a valid approach for treating fatigue in breast cancer patients, as evidenced by the results of a meta-analysis of 10 randomized trials [24].

3.1.4. Pharmacological interventions
Several psychostimulant drugs have been investigated in the management of cancer-related fatigue, such as methylphenidate, dexmethylphenidate, long-acting methylphenidate, dexamphetamine, modafinil, and armodafinil. Most studies showed no advantage of psychostimulant drugs over placebo, while three studies with methylphenidate (5–30/40 mg

Table 1. Summary of main management strategies.

Side effect	Prevention	Management	References
Fatigue	N/A	Non-pharmacological: • Moderate intensity exercise • Cognitive-behavioral therapy • Yoga Complementary medicine: • Wisconsin Ginseng • Acupuncture Pharmacological: • Methylphenidate: 5–30/40 mg • Dexmethylphenidate: 10–50 mg/day	[14, 15] [18] [20, 21][22] [24][25–27] [28]
Insomnia	N/A	Non-pharmacological: • Moderate intensity exercise • Yoga [57, 58] • Cognitive-behavioral therapy Pharmacological: • Lorazepam: 1–2 mg/day • Zolpidem: 10 mg/day • Melatonin: 6 mg/day	[58, 59] [62, 63] [64–66][72] [72] [73]
Peripheral neuropathy	• Exercise • Functional training	Non-pharmacological: • Moderate intensity exercise • Functional and balance training Complementary medicine: • Acupuncture Pharmacological: • Duloxetine: (30 mg/day for 1 week, then 60 mg/day for 4 weeks) • Venlafaxine (37.5 –225 mg daily) • Amitriptyline (10 –50 mg/day)	[85, 88] [88][86] [90] [91] [92] Prevention: [75, 82]
Cognitive Impairment	N/A	Non-pharmacological: • Relaxation and mindfulness training • Moderate intensity exercise • Brain-training computer programs Pharmacological: • Modafinil (200 mg day for 4 weeks) • Donepezil (5 mg/day for 6 weeks, then 10 mg/day for 18 weeks)	[107, 108] [109] [110][112] [113]
Fertility and sexual health	• Embryos/oocytes/ovarian tissue cryopreservation • Gonadotropin-releasing hormone agonist • Vit. D supplementation and regular exercise (for bone health)	Non-pharmacological: • Cognitive behavioral therapy • Non-hormonal vaginal lubricants • Vaginal dilators (associated with pelvic floor exercises) • Physical exercise and yoga Pharmacological: • Gabapentin (900–2,400 mg/day) • Venlafaxine (37.5 –75 mg/day)	[119, 120] [119, 120] [119, 120][124, 125][132] [134] Prevention: [117, 118, 139]
Cardiotoxicity	• Correction of basal risk factors • Liposomal formulations • Dexrazoxane (1 mg for each 10 mg of doxorubicin, given at least 30 min prior to each doxorubicin infusion) • Enalapril (2.5– 20 mg daily) • Candesartan (32 mg q.d)	Treatment suspension and cardiologist evaluation for initiation of a cardioprotective treatment.	Prevention: Liposomal formulations: [155–158] Dexrazoxane: [159, 160] Enalapril: [166] Candesartan: [167]

day) and one with dexmethylphenidate (10–50 mg/day) reported an improvement in CRF [25–28]. A subgroup analysis of two different studies suggested a benefit of long-acting methylphenidate and modafinil [29,30]. Considering the mostly negative results of these studies, ESMO guidelines do not advise routine use of psychostimulant drugs, with potential exceptions, such as use of methylphenidate, dexmethylphenidate, long-acting methylphenidate, and dex-amphetamine in thoroughly selected patients [8]. Paroxetine, donepezil, eszopiclone, megestrol acetate, and melatonin have not been proven to be effective [31–36].

There is currently lack of evidence about use of steroids for long-term fatigue in early breast cancer, which, overall, is not advisable due to their mid- and long-term side effects [8]. A double-blind, placebo-controlled trial is currently ongoing, testing the effectiveness in this setting of a 13-week treatment with bupropion [37].

4. Insomnia

Insomnia, fatigue, and depression are often related and act synergistically to worsen each other and to lower QoL [38–41]. Sleep disruption is prevalent during and after chemotherapy [42,43]. While treatment anxiety may contribute to the onset of insomnia, physical symptoms (such as pain and vasomotor syndrome) can cause sleep disruption during chemotherapy and may persist even after completion of treatment [44]. Circadian rhythm disruption has been associated to a shorter overall survival (OS) in BC patients [45], and to a higher incidence of cognitive impairment and metabolic disruption [46,47].

4.1. Management

4.1.1. Screening and prevention
Three groups of etiological factors have been recognized in cancer-related insomnia [48]:

- Predisposing factors (pre-existing and non-modifiable), such as gender, younger age, and a history of psychiatric disorders.
- Precipitating factors: psychological and physical effects related to cancer diagnosis and treatment (i.e. stress, pain, use of corticosteroids during chemotherapy).
- Perpetuating factors: sleep behaviors which, due to a maladaptive mechanism, contribute in maintaining a state of sleep disturbance (i.e. sleeping in the afternoon rather than overnight).

Development of sleep disturbances seems to be related to a disruption of the circadian rhythm [49], possibly due to a flattened curve of cortisol secretion. Overweight also can furtherance the propagation of a low-grade chronic inflammatory status, thus contributing to perpetuating the sleep disruption through an increased release of cytokines [50–52]; an association between obesity, sleep disruption, and fatigue has indeed been reported [53–56].

There is a dearth of evidence about the association between cancer-related post-traumatic stress disorder (PTSD) and insomnia, although PTSD and insomnia have been associated in non-cancer research [57].

No prevention strategy has been recognized.

4.1.2. Non-pharmacological interventions
Moderate intensity exercise improves both sleep quality and circadian resynchronization [58,59]. However, there is a scarcity of evidence about physical intervention in cancer patients [60,61]; available data show the potential usefulness of Yoga [62,63].

In BC survivors, cognitive behavioral therapy for insomnia (CBT-I) improves the quality of sleep up to 12 months [64–66]. Yet, CBT-I is a difficult treatment to implement routinely, as it requires mental health professionals formally trained in this approach.

Other behavioral interventions, such as sleep hygiene education and sleep restriction treatment, have been tested with mixed results [67–70].

Controlled bright light exposure could be useful in improving sleep disruption and fatigue in breast cancer patients, by targeting the resynchronization of the biological clock [71].

4.1.3. Pharmacological interventions
Lorazepam and zolpidem are commonly prescribed to treat insomnia [72]; however, there is no evidence on prolonged use to address long-term sleep disruption following treatment for breast cancer.

A small randomized trial enrolled 95 BC survivors to receive either melatonin 6 mg or placebo after treatment, with promising results [73].

5. Peripheral neuropathy

Many standard chemotherapy regimens in EBC, including platinum agents and taxanes, can induce chemotherapy-induced peripheral neuropathy (CIPN), which may persist even years after completion of treatment [74–76]. In a systematic review, the estimated frequency of persistent CIPN 1 or more years post-treatment ranged from 11.0% to >80% [77].

Incidence, severity, and clinical pattern of CIPN depend on the individual antineoplastic drug [75,78,79]; it results in a predominant sensory axonal involvement (i.e. paresthesias, pain, muscle weakness, and ototoxicity), but sometimes it can occur as motor (i.e. reduction/absence of deep tendon reflexes, distal weakness and muscular atrophy, tremor, cramps) and autonomic dysfunction (i.e. abdominal pain, constipation, delayed gastric emptying, postural hypotension, reduced variability of heart rate and bladder disturbances) [74,75]. More distinctive symptoms are taxane-induced myalgias and cranial nerve palsy following the administration of vinca alkaloids [74]. All platinum salts are characterized by the phenomenon of "coasting," which consists in a worsening of symptoms in the months following the completion of the treatment [74].

A summary of the clinical presentation of the main neuropathic drugs is presented in Table 2.

Table 2. Summary of clinical presentation of the main chemotherapy drugs for breast cancer inducing CIPN.

Drugs	CIPN incidence (%)	Clinical presentation and specific features	References
Carboplatin	G 1–4: 10–27%	Paresthesia, ataxia, mild pain; less frequent and severe than other platinum compounds, mostly in higher doses.	[74]
Vincristine	G 1–4: 35–61%	*Sensory*: pain and temperature sensation. *Autonomic*: constipation, less frequently orthostatic hypotension, bladder dysfunction and impotence. Early manifestation (after 3 doses): Raynaud syndrome. *Motor*: mononeuropathies including tibial and peroneal nerves, distal weakness, cranial nerve palsy. Rarely Guillain–Barrè Syndrome, very occasionally accompanied by fulminant tetraplegia	[74]
Docetaxel	G 3/4: 10%	Pain, paresthesias, loss of temperature sensation, loss of proprioception with ataxia.	[78]
Paclitaxel	G 3/4: 20–35% (250 mg/m^2 every 3 weeks) 5–12% (≤200 mg/m^2 every 3 weeks	Proximal weakness with concomitant sensory neuropathy (17%)	[78]
Nab-paclitaxel	G 3/4: 9% (100 mg/m^2 days 1, 8, 15 every 4 weeks) to 21–22% (300 mg/m^2 every 3 weeks and 150 mg/m^2 days 1, 8, 15 every 4 weeks, respectively)	Acute: *Paclitaxel*: musculoskeletal pain within 72 h in up to 60% of patients, (painful arthralgias, axial- and limbs myalgias) *Docetaxel*: arthralgias nab-paclitaxel: shorter time to improvement after completion of chemotherapy	[79]

• CIPN: chemotherapy-induced peripheral neuropathy. G: Grade (as defined by the Common Toxicity Criteria for Adverse Events (CTCAE) scale).

5.1. Management

5.1.1. Screening and prevention
Screening relies on identification of individual risk factors, which could affect the choice of chemotherapy; individual risk factors include age (≥75 years), gender, previous treatments, pre-existing peripheral neuropathy and diseases/deficiencies predisposing to neuropathy (i.e. alcohol abuse, diabetes, renal insufficiency, hypothyroidism, vitamin deficiency, infections, autoimmune rheumatologic conditions) [74,75]. In patients with advanced BC aged ≥65 years, the EFFECT phase II trial demonstrated that, with the same schedule, nab-paclitaxel 100 mg/m^2 was associated with fewer neurotoxicity-related events than nab-paclitaxel 125 mg/m^2 [80]

Early detection of CIPN can be achieved by performing baseline and ongoing clinical evaluations of physical function, followed, if needed, by complementary neurophysiological investigations [75,81]. Sleep disturbance, anxiety, depression, and central sensitization of pain may aggravate neuropathic pain [75].

Till date, there is no effective pharmacological agent to prevent CIPN [75]. Among non-pharmacological prevention, only exercise and functional training can be recommended [75,82]. Acupuncture is discouraged, while cryotherapy is still debated: in the largest randomized phase III trial evaluating frozen gloves, no difference in CIPN subscales was demonstrated between the two arms. Besides, about one-third of the frozen gloves group discontinued the treatment [83].

5.1.2. Non-pharmacological interventions
Physical exercise and functional training (i.e. vibration training) could be considered [82,84,85]. For patients receiving taxane-, platinum-, or vinca alkaloid-based chemotherapy, Kleckner et al. reported a statistically significant reduction of CIPN symptoms with exercise compared to the control group, especially for older patients, male, or BC survivors [84,85].

In a recent small, randomized pilot trial of 40 BC survivors, an 8-week acupuncture intervention demonstrated an improvement in subjective sensory symptoms [86]. Implementing falls prevention strategies in patients with an increased risk of falling due to lower leg paresthesia is also essential [87]. Bao et al. demonstrated that severity of CIPN was directly associated with a higher rate of falls [76]. A recent systematic review demonstrated a good level of evidence for physical exercise, balance, and sensorimotor training, but only inconsistent evidence in use of cryotherapy, compression therapy, massages and related activities, and electrical stimulation [88]. There is also some scant evidence regarding the use of photobiomodulation [89].

5.1.3. Pharmacological interventions
Relief of neuropathic pain is the main objective of treatment. According to ESMO guidelines, duloxetine (30 mg/day for 1 week, then 60 mg/day for 4 weeks) is the only drug recommended for treatment of neuropathic pain [90], while venlafaxine (37.5 mg b.i.d.), and amitriptyline (10 –50 mg/day) could be considered [91,92]; tramadol or strong opioids could represent a salvage strategy in the management of neuropathic pain [75]. Antioxidants have shown their efficacy in treating CIPN in several clinical trials [93]. Although almost all of these trials did not focus on a specific subtype of cancer, BC patients represented a significant percentage of the patients enrolled; the exception is the EFFOX trial [91], where the majority of patients were affected by a gastrointestinal cancer; the advice for the use of venlafaxine, therefore, should be considered with attention, as it is extrapolated by a trial non directly regarding breast cancer survivors. A dedicated study should be performed, to assess the efficacy of this intervention in this subset of patients.

5.1.4. Complementary medicine

Dietary supplements represent a growing research field, such as vitamins (group B and E), acetyl-L-carnitine, unsaturated fatty acids, extracts of medical plants (goshajinkigan, curcumin, etc.) [89,94]. However, evidence is still scant and needs to be implemented to confirm a potential action against CIPN.

6. Cognitive impairment

Cognitive impairment affects up to 70% of non-CNS (central nervous system) cancer patients during or after chemotherapy [95]; this phenomenon is commonly known as 'chemobrain' or 'chemofog.' In breast cancer, it is estimated that chemobrain can affect from 17% to 75% of cancer survivors [96].

The term 'chemobrain' refers to a constellation of disorders that mainly concern the sphere of short-term memory, attention, learning, verbal ability, executive functions, and motor activities [97–99]. The natural history of chemobrain comprises an onset phase, an acute phase, and finally a partial or complete recovery phase [100].

Moreover, hormonal deprivation, secondary either to chemotherapy-induced menopause or to anti-hormonal treatments, could worsen patients' cognitive functions. However, the scarce scientific evidence available is conflicting [101–103]

Results from a randomized clinical trial comparing cognitive function in three different groups of BC patients treated with different types of chemotherapy showed an independent, direct dose-related effect on cognitive function [104]

6.1. Management

6.1.1. Screening and prevention

Patients often do not report chemobrain to their oncologists, probably due to lack of awareness. At the same time, routine assessment of cognitive functions is not routinely performed, except within clinical trials. Several assessment tools have been proposed; these include the Wechsler Memory Scale (WMS), which is a verbal memory test; the Wechsler Adult Intelligence Scale (WAIS), which can identify even small changes in cognitive functions; the Mini Mental State Examination (MMSE), and some neuropsychological methods, such as the High Sensitivity Cognitive Screen (HSCS) [105]. However, none of these has been established as the reference tool. Functional magnetic resonance imaging (fMRI) identified structural cerebral alterations – decrease in both the gray matter in the neocortex and cortex and in the white matter at the subcortical level – in patients with changes in neuropsychological tests [106].

Increasing the awareness of this phenomenon both in doctors and in patients would allow early identification of signs and symptoms, to monitor their evolution over time and to facilitate the implementation of the aforementioned strategies.

To date, there are no known preventive strategies nor approved therapeutic interventions. Yet, a treatment strategy combining behavioral with psychopharmacological approaches could be considered.

6.1.2. Non-pharmacological interventions

Behavioral interventions include

- Relaxation and mindfulness training [107,108]
- Physical exercise to improve processing speed in BCS and enhanced neurogenesis [100,109]
- Occupational therapy to recover or maintain daily and working life skills through activity
- Brain-training computer-based programs to increase memory and processing speed [110]
- Electroencephalography (EEG) biofeedback to improve cognitive indexes, fatigue, sleep, and psychological scales [111]
- Lifestyle changes: using a detailed planner; getting enough rest; accepting support from relatives and friends; avoiding alcohol or other substances that could alter the mental state.

6.1.3. Pharmacological interventions

Despite the lack of data from randomized clinical trials, drugs that could be considered are

- Central nervous system (CNS) stimulants: modafinil (200 mg day for 4 weeks) has shown potential in improving cognitive functions [112]
- Donepezil: a reversible acetylcholinesterase inhibitor used in patients with Alzheimer disease, which improves memory and attention in patients affected by brain cancer (5 mg/day for 6 weeks, then 10 mg/day for 18 weeks) [113]
- Antidepressive drugs, such as fluoxetine, or mood stabilizer drugs, such as lithium, appear to increase neurogenesis, especially in the hippocampus [100]

7. Estrogen deprivation side-effects – fertility and bone health

Modern chemotherapy regimens hinder the normal ovarian function; complete ovarian failure occurs in more than half of BC patients who undergo chemotherapy in their forties and in 15–30% of patients younger than 35 years [114,115]. Use of alkylating agents, such as cyclophosphamide, is associated with a higher risk of ovarian failure, while anthracyclines and taxanes have an intermediate risk [116].

Chemotherapy-induced premature ovarian failure often elicits the side effects of estrogen deprivation, which can be magnified by a concurrent endocrine therapy. Psychological and physical side effects comprise vasomotor symptoms, musculoskeletal pain, sexual dysfunctions, sleep deprivation, and depression, often more intense of those occurring during physiological menopause. Early iatrogenic menopause also influences bone health, disrupting the balance between bone formation and reabsorption.

7.1. Management

7.1.1. Prevention

Patients who are interested in preserving their fertility can undergo embryos, oocytes, or ovarian tissue cryopreservation prior to commencement of chemotherapy; however, these procedures are not always feasible due to time requirements, which are not always appropriate while commencing a primary treatment for a rapid growth type of cancer. Besides, embryos and oocytes preservation is not a treatment for prevention of premature ovarian insufficiency. In contrast, there is some limited evidence that ovarian tissue cryopreservation can allow ovarian function recovery [117]. Another opportunity is represented by concomitant administration of gonadotropin-releasing hormone agonist (GnRHa) along chemotherapy, which protects ovarian tissue through different mechanisms, and it is not contraindicated in women who undergo cryopreservation procedures. GnRHa induces, however, a temporary suppression in ovarian function, thus eliciting menopausal symptoms [117,118]

7.1.2. Non-pharmacological interventions

- Sexual disorders secondary to iatrogenic menopause can be managed with behavioral or non-hormonal intervention. Many trials suggested the benefit of cognitive behavioral therapy in breast cancer survivors, especially in those who experiment sexual dysfunction, intensified by adjuvant endocrine therapy. SHARE-OS trial highlighted an improvement in sexual health in women who received ovarian suppression by undertaking body awareness exercises and mindfulness-based therapy. In addition, given their availability and low-cost, non-hormonal vaginal lubricants, such as topic lidocaine, or vaginal dilators associated with pelvic floor exercises, should be advised to handle dyspareunia and vaginal dryness [119,120]. Vaginal laser therapy (CO_2 or erbium) showed positive effects on genitourinary symptoms, but its use is controversial due to the lack of randomized trials with a long-term safety follow-up and to the high costs of this treatment [121–123].
- Vasomotor symptoms, typical of chemotherapy-induced menopause, can be managed with non-pharmacological strategies, such as weight maintenance, regular physical exercise, yoga, relaxation exercises, and acupuncture [124,125].

7.1.3. Pharmacological interventions

- There is uncertainty about the safety of local estrogen or testosterone-based therapies; several studies showed an increase in serum estradiol levels, despite the lack of evidence of increased risk of recurrence [126]. A more recent trial, however, assessed the safety and effectiveness of ultralow 0.005% estriol vaginal gel in a small group of 61 women with BC having treatment with nonsteroidal aromatase inhibitors; no significant difference in FSH, LH, and estradiol were observed; a transient and minimal absorption of estriol was observed at the beginning of treatment [127].

- Hormone-replacement therapy is the most effective treatment for estrogen-deficiency symptoms, but it is contraindicated because of the risk of breast cancer recurrence, as shown in the HABITS, Stockholm, and LIBERATE trials [128–130]. Furthermore, some preclinical studies showed that ospemifene, an oral selective estrogen receptor modulator effective for the management of vaginal dryness, has an anti-estrogen activity on breast cancer cells, but due to the lack of safety data, its use in this setting is to date not recommended [131].
- Most severe cases of vasomotor symptoms require use of SSRI/SNRI antidepressant or anticonvulsant drugs such as gabapentin, pregabalin, or clonidine [132,133]. Venlafaxine (37.5 –75 mg/day) is the most studied agent for preventing hot flashes, but higher doses can cause loss of appetite, mouth dryness, nausea, and constipation [134]. Similar efficacy, with a slightly different profile of side effects, is given by gabapentin (900–2,400 mg/day) and pregabalin. On the other hand, clonidine, an α-adrenergic agonist, has been shown to be less effective than venlafaxine [135]. Oxybutynin, an anticholinergic drug, improves hot flashes in women with or without breast cancer [136].

As for bone health, many trials demonstrated that both bisphosphonates (zoledronic acid, alendronate) and denosumab (a monoclonal antibody directed against RANKL) improve bone mineral density in women with osteoporosis or subjected to treatment with drugs capable of undermining bone health [137]. The duration of anti-resorptive treatment is controversial and is usually related to the persistence of a high fracture risk. There is also evidence that the use of bisphosphonates is associated to a reduction of bone recurrence, in particular in postmenopausal women [138]. Women should also be advised to adopt a lifestyle that promotes bone health, undergoing regular physical exercise to prevent bone loss; according to ESMO and NCCN guidelines, calcium and vitamin D supplementation is warmly recommended [139,140].

8. Cardiotoxicity

The term *cardiotoxicity* comprises a large spectrum of clinical entities, including cardiac dysfunction, ischaemia, vascular disorders, endothelial damage, and arrhythmias. Chemotherapy toxicity is rarely dependent on a single mechanism. Besides, long-term toxicities and cardiovascular (CV) comorbidities, pre-existing or related to aging, may overlap, and consequently increase patients' morbidity [141].

In breast cancer patients, we broadly differentiate three categories of cardiovascular impairment, according to the related drug: *anthracycline-induced cardiotoxicity*, *non-anthracycline agent-induced cardiotoxicity*, and *anti-HER2 therapy-related cardiotoxicity*.

8.1. Anthracycline-induced cardiotoxicity

Anthracyclines (AC) are a mainstay of treatment for BC [142–145]. AC detrimental effect on cardiac function is well recognized and represent the dose-limiting adverse event of this

therapy. AC-induced cardiotoxicity essentially entails a decreased left ventricular ejection fraction (LVEF) with a rising risk of congestive heart failure (CHF).

8.1.1. Screening

The main risk factor is represented by cumulative dose (over 450–550 mg/m^2 of doxorubicin and 900 mg/m^2 of epirubicin) [146,147], but pre-existing cardiovascular diseases, obesity, diabetes mellitus, hypertension, smoking habit, age greater than 65 years, anti-HER-2 agents and chest irradiation increase the susceptibility to cardiac damage [148]. AC-induced cardiotoxicity should be suspected in the presence of CHF symptoms, such as declivous edema, dyspnea, and syncope, but requires echocardiographic evidence of decreased LVEF (<10% than basal, absolute value <53%) [149]. Testing circulating biomarkers, such as troponin, could reveal a preclinical myocytic damage and predict an HF diagnosis [150].

Several studies have demonstrated that early detection and treatment allow a functional recovery; conversely, a delayed diagnosis leads to a lack of response to treatment [151,152].

Every patient should undergo a baseline cardiological evaluation, comprising ECG and echocardiography (ECHO) before starting AC-treatment. If chemotherapy with doxorubicin doses <200 mg/m^2 is planned, patients should be reassessed at the end of treatment and every 6 months for the first year. Additional follow-up should be modulated on basal risk [153].

8.1.1. Prevention

Primary prevention, such as correction of CV basal risk factors (i.e. smoking habits, hypertension, and dyslipidaemia), is fundamental. In addition, liposomal formulations and continuous infusion instead of bolus dosing reduce direct AC cardiotoxic effect [154–158]. The most investigated cardioprotective drug is dexrazoxane, which showed benefits both in reduction of HF risk and subclinical cardiotoxicity [159,160]. Although it was initially suspected of reducing AC efficacy and inducing secondary malignancies, recent literature has assessed its safety and dexrazoxane is approved by regulatory agencies for patients exposed to previous cumulative doses of doxorubicin >300 mg/m^2 or epirubicin >540 mg/m^2 [158,161,162]. Therefore, dexrazoxane (1 mg for each 10 mg of doxorubicin, given at least 30 minutes prior to each doxorubicin infusion) should be considered in patients with either a high cardiovascular risk, or about to receive a high total cumulative anthracycline dose for curative treatment. The role of neurohormonal antagonists, such as angiotensin-converting enzyme inhibitors (ACEi), angiotensin II receptor blockade (ARB), and aldosterone antagonists, is not well established for patients with a low CV risk [141,153]. Two meta-analyses reported a benefit in preventing LVEF reduction with the use of cardioprotective drugs (renin–angiotensin–aldosterone system blockers, beta-blockers, aldosterone antagonists, ACE inhibitors) [163,164]; however, there was no statistically significant benefit in the incidence of heart failure and adverse clinical effects. A different meta-analysis confirmed the benefit in protecting the LV systolic function for a combination of candesartan and carvedilol, spironolactone, enalapril, and statins [165]. A trial showed the efficacy of enalapril (2.5 –20 mg daily) in preventing left ventricular dysfunction in patients with an elevation in troponin value during or after chemotherapy [166]. Authors in the PRADA trial proved the role of candesartan (32 mg q.d.) in reducing the decline in LVEF [167]. Globally, neuro-hormonal therapies seem to reduce LVEF dysfunction with a trend of statistical significance [161]. Finally, third-generation beta-blockers (i.e. carvedilol and nebivolol) showed cardioprotective properties preventing a decrease in LVEF and left ventricular enlargement [168–171]; a meta-analysis showed a reduction in clinically detectable cardiotoxicity with the prophylactic use of beta-blockers, although there was no improvement in the incidence of early asymptomatic LVEF decrease [172]. The 2022 ESC guidelines on cardio-oncology suggest considering ACE-I, ARB, beta-blockers, and statins for primary prevention in high- and very high-risk patients receiving cancer therapies that may cause heart failure [158]. Patients who presented with signs or symptoms of cardiac dysfunction during or after chemotherapy should be treated according to guidelines for HF [141].

8.2. Non-anthracycline agents

Cardiotoxicity is associated with other antineoplastic agents commonly used in early BC, such as cyclophosphamide, 5-fluorouracil, platinum, and taxanes, is less frequent, typically not dose-related, and characterized by an early onset. Due to the intent of this review, acute cardiotoxicity will not be analyzed extensively. In summary, the main toxicities reported are cardiac ischemia, rhythm disturbances (QTc prolongation, arrhythmia, sinus bradycardia), coronary vasospasm, and vasospastic angina [173,174].

Considering the low incidence, no cardiac monitoring or prophylactic therapy are routinely required [175].

8.3. Anti-HER2 therapy-related cardiotoxicity

HER2 pharmacological blockade may induce cardiac alterations, resulting in structural and functional changes which manifest clinically with a decline in LVEF and CHF [176]. Trastuzumab therapy in the adjuvant setting had a relative risk (RR) of 5,1 for impaired LVEF and 1,8 for CHF [177]. Seidman and colleagues found a higher rate of cardiotoxicity in those patients who underwent AC-based chemotherapy concomitantly (27% for combination therapy, 8% for CT alone) rather than sequentially [178–180].

Previous history of exposure to AC, especially if recent, BMI >25 kg/sqm, low basal LVEF, older age, and duration of treatment >1 year are known risk factors for trastuzumab-induced cardiotoxicity [141,175–177,181–184]. Recognition of risk factors, careful selection, and adequate and periodic cardiac follow-up allowed to reduce the incidence of cardiotoxicity [176].

Treatment suspension represents the main intervention to allow functional cardiac recovery, whereas the role of HF drugs is still controversial [141,185].

In adjuvant setting, CV assessment consists of ECHO every 3 months or more frequently if clinically indicated. Throughout the treatment, a value of LVEF between 40% and 49% requires a cardiologist evaluation and initiation of a cardioprotective

therapy (i.e, ACEi or ARB). A decrease in LVEF > 15% should prompt discontinuation of trastuzumab; cardiac function should be reassessed every 4–6 weeks until an LVEF >50%.

Anti-HER2-associated toxicity has often an early onset and is mostly reversible; thus, a specific CV follow-up is not required; an elevation of troponin could be a predictor of LVEF reduction and poor cardiac outcome, identifying a group of patients less likely to recover from cardiotoxicity [186].

Other anti-HER2 drugs, such as pertuzumab, trastuzumab-metansine (T-DM1), and lapatinib showed a lower CV toxicity profile. In particular, the addition of pertuzumab to trastuzumab is not associated with higher toxicity [187–190].

9. Second cancers

The association between chemotherapy and acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) is well known [191–194]. In general, topoisomerase II inhibitors, cyclophosphamide, and platinum compounds possess a leukemogenic potential [194–197]. The risk of AML and MDS appears to peak 2–5 years after chemotherapy, with a decline after 10 years [191]. Pancytopenia, marrow failure, or myelodysplasia are often the first signs recognized. Chemotherapy-related AML/MDS are often characterized by a poor prognosis, due to an intrinsic drug resistance [191].

Alkylating drugs have been also linked to an increased risk of a wide range of solid malignancies, especially lung cancers, gastrointestinal cancers, sarcoma, and bladder cancers, with a dose–response relationship [191,198,199]. Similarly, topoisomerase II inhibitors may increase the risk of new breast cancers [199]. The rate of development of chemotherapy-related solid cancers seems to persist even for decades [199]. Nothing is known about the long-term carcinogenic potential of targeted therapies.

The genesis of a second cancer is unpredictable and up to date there are no effective prevention tools. Henceforth, especially in heavily pretreated patients, strategies to favor the adherence to national cancer screening programs should be implemented. A careful and timely clinical evaluation remains, to date, the cornerstone of early detection of second neoplasms.

10. Conclusion

In our review, we aim to provide a comprehensive summary of the most common long-term side effects and their management. We found that some symptoms are often unrecognized, and there is a dearth of prevention strategies and standardized screening systems. Although few data on pharmacological agents exist, there is evidence that lifestyle approaches are often the best management strategy.

11. Expert opinion

Long-term survivorship, in oncology, is a relatively new and scarcely explored, although substantial, field. Thanks to the screening programs and the advances in anticancer therapy, the number of cancer survivors is increasing overtime.

However, such a population may present treatment-induced chronic ailments that generate a public health problem to be addressed in a consistent way.

Most treatments in oncology, when assessed for safety, are evaluated on the basis of acute side effects, rather than chronic issues that, although less life-threatening, can significantly affect the quality of life of the survivors for the years to come. Follow-up of oncology patients is often solely aimed to assess recurrence, rather than addressing other issues which are, sometimes, even unrecognized (like insomnia and cognitive impairment). With the increasing number of survivors, especially in breast cancer – the most common cancer in women – the need to address such symptoms in a more coherent way is starting to emerge.

This review focuses on the practical management of long-term toxicities. In the real world, often these toxicities are managed empirically, when addressed at all. The aim of our study is to provide an evidence-based, comprehensive, pragmatical basis for management of these symptoms, thus improving the real-world long-term quality of life outcomes of breast cancer survivors. Changes in current practice would require, in first instance, a shift of paradigm to focus not only on the mere survival of these patients but on their quality of life and the challenges issued in daily life by the residual toxicities of the treatments they underwent. We propose several measures that could be implemented; while some of them would require additional funding and availability of trained health-care professionals, others could be more easily adopted by most breast cancer centers.

The first measure to be implemented should be increased education for both patients and health-care operators. This would equally increase the capability of patients to recognize and, therefore, report significant symptoms and the ability of health-care providers to intervene in an appropriate way, being aware not only of the problem but also of the potential treatments available, which are not confined to pharmacological options.

Management of symptoms, in oncology, has often been delegated to palliative care; in our opinion, supportive care needs to be routinely implemented in breast cancer centers. Moreover, as the beneficial effects of exercise are recognized in many fields, dedicated facilities could be helpful in implementing a routine pattern of exercise in breast cancer survivorship.

A phone-based nurse-monitoring intervention has been proven effective in reducing the severity and the duration of different treatment side effects; in cases where a supportive care clinic cannot be implemented due to lack of resources (either financial or in terms of staff availability), a nurse-led phone-based follow-up clinic could be effective and easier to establish.

We recognize as key areas for improvement the standardization of assessments and treatments, patients and health-care providers education, and implementation of supportive care clinics associated with breast cancer centers. Most of the symptoms we discussed do not have any recognized prevention strategy; moreover, there is lack of standardization in their respective scoring systems, which are scarcely used in clinical practice. This is a poorly explored area for research; further

studies would be needed to identify reliable and easy-to-use scoring systems, and subsequently effective prevention strategies.

We found that the most useful management strategies are often lifestyle and behavioral interventions; these should be routinely discussed with patients. However, these interventions often require the support of specifically trained healthcare operators, which are few and not always available; ideally, all breast cancer centers should have a referral system to a specific supportive care clinic. Whenever lifestyle and behavioral interventions are not possible, a pharmacological approach could be considered, with the aim of minimizing the number of different medications taken and therefore choosing, whenever possible, medications that will have a beneficial effect on more adverse events at the same time (i.e. venlafaxine for peripheral neuropathy and vasomotor syndrome).

In our opinion, improvements in this field, in the next few years, should focus on two main aspects. First, as there is a dearth of prevention strategies for most of these symptoms, a research effort should be considered to establish clear and effective protocols to be empowered in the clinical setting. In second place, we believe that specific clinics for treatment of cancer treatments long-term side effects should be implemented and available to all breast cancer centers, or, alternatively, that specific education should be given to patients and health-care operators. As the survival rate of patients increases, so does the need for an evidence-based optimization of survivorship management; in the next few years, dedicated clinics should become increasingly common, and referral to dedicated training and exercise programs tailored on these patient-specific needs should become available in most breast cancer centers.

Author contribution statement

Conceptualization: P Di Nardo and F Puglisi; investigation: P Di Nardo, C Lisanti, M Garutti, S Buriolla, M Alberti, and R Mazzeo; writing: P Di Nardo, C Lisanti, M Garutti, S Buriolla, M Alberti, and R Mazzeo; supervision: F Puglisi. All authors have read and agreed to the published version of the manuscript.

Declaration of interests

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