Adverse effects in the management of breast cancer – recent studies

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Abstract
Introduction and purpose
Breast cancer (BC) management includes local therapies surgery, radiotherapy and systemic – hormonotherapy, chemotherapy, targeted and immunotherapy. However, some adverse events of these treatment strategies limit their wide administration in BC therapy. The aim of the study was to present adverse effects in the management of BC, prevention and treatment of them.
State of the knowledge
Surgery of the breast leads to lymphedema, pain, and anatomical changes. The most characteristic adverse event of radiotherapy is radiation dermatitis which is more probable among obese, older patients, females, and smokers. Other side effects are pneumonia, cardiac and pulmonary injury. Chemotherapeutics lead to complications such as anthracyclines-induced cardiotoxicity. As a consequence of endocrine therapy, patients are affected by vasomotor, musculoskeletal, and vulvovaginal symptoms. Immune checkpoint inhibitors may cause immune-related adverse events (irAEs), which are usually mild. When severe irAEs occur, immunosuppressive drugs are used. Depending on stage, toxicities of the therapies can lead to interrupting the treatment of BC. Moreover, drug resistance is an important therapeutic obstacle in BC treatment.
Conclusion
The application of a diversity of drugs in the treatment of breast cancer is associated with adverse effects which limit its efficacy. It is vital to develop novel, targeted therapeutic methods to optimize outcomes of patients. Given the adverse effects of breast cancer therapies and drug resistance, it is vital to develop novel, targeted therapeutic methods.

Keywords: Breast cancer; Breast cancer treatment; Radiotherapy; Immunotherapy; Toxicity; Chemotherapy

Introduction and purpose
Currently, breast cancer (BC) is the most noted female cancer worldwide, accounting for 2.3 million new cases annually, and the main cause of cancer-related death [1]. BC treatment and outcomes are getting improved due to advances in screening – tumor detection in early stage and effective, multimodality care [2,3]. BC treatment choice requires an individual approach, taking into account factors related to a patient, stage of disease, and cancer molecular subtype. In early-stage BC, surgery is a first-chose therapy. The surgical management of BC involves breast-conserving surgery (BCS), mastectomy (including skin-sparing and nipple-sparing types) and modified radical mastectomy [4]. Each surgical method is associated with different rates of surgical morbidity and complications. Radiation following mastectomy in patients with positive lymph nodes is associated with improved survival rates compared to patients with negative lymph nodes [5]. Whether human epidermal growth factor receptor-2 (HER2) is expressed on cancer cells, it is possible to use anti-HER2 agents [6]. Endocrine therapy is used among patients with positive receptors tumors – estrogen receptor (ER) positive and/or progesterone receptor (PR) positive [7]. In adjuvant therapy, the most commonly used selective estrogen receptor modulator (SERM) – tamoxifen is administered independently on menopause status, while aromatase inhibitors are used in postmenopause patients [8]. Luteinizing hormone-releasing hormone (LH-RH) analogues should be given as adjuvant therapy and after recurrences in women before menopause. In HER2-positive and triple-negative tumors, it is worth considering neoadjuvant chemotherapy [9]. Chemotherapy is given as neoadjuvant or adjuvant treatment or for metastatic BC [10]. Systemic adjuvant therapy is used in aim to control deposit of disease, and reduce recurrence.
rates [11]. Combination chemotherapy consequences in better efficacy and decreased toxicity compared with monotherapy. Cytotoxic drugs such as taxanes (docetaxel, paclitaxel), anthracyclines (doxorubicin, epirubicin, pegylated liposomal doxorubicin), and capecitabine are the most common therapeutics as monotherapy in metastatic BC [12]. Furthermore, the next treatment method – immunotherapy has shown clinical value in trials and has promising efficacy in BC. This therapeutic option is associated with clinical activity and benefits if the cancer is triple negative, tumor cells express PD-L1, and/or are higher levels of tumor-infiltrating lymphocytes (TILs) [13]. Immune checkpoint inhibitors (ICI) – atezolizumab and pembrolizumab comprise promising drugs in triple-negative breast cancer (TNBC) therapy [14].

Adverse effects of systemic therapies can negatively impact health-related quality of life (HR-QOL), so it is important to assess its frequency, risk factors and develop preventive strategies [2]. Additionally, due to BC prevalence, it is important to be aware of the advantages and adverse effects of both local and systemic treatment methods, their symptoms and diagnosis. Adverse effects can affect BC patients quality of life. Moreover, depending on stage, it can interrupt the treatment of the base disease.

The aim of the study was to present adverse effects in the management of breast cancer, prevention and treatment of them.

State of the knowledge

Surgery

Generally, surgery of the breast and axillary is specified by low risk of complications [4]. However, it can cause pain, lymphedema, seroma, hematoma, infections, and skin necrosis. Long-term adverse effects of surgery are anatomical changes, chronic pain, phantom breast pain or lymphedema [15]. Seroma production is one of the characteristic side effects of the surgery, which can delay radiation therapy and impact the well-being of the patient [16, 17]. Seroma production affects 3 to 85% of patients after breast or axillary surgeries [18]. Electrocautery used to seal vessels and stop blood loss contributes to tissues injury via heat action, so it is not a proper method for prevention of seromas [19]. Seromas often fluctuate, but when they are large, tense, or a reason for discomfort, recommended removal method is aspiration [20]. However, multiple injections increase the risk of infection. In case of chronic seromas, hypertonic saline and iodine were used as seromasis. To reduce seroma formation, tightening the flap after surgery is the promising method [21]. Serious postoperative complications such as paresthesia and lymphedema are more frequent after axillary lymph node dissection (ALND) than sentinel lymph node biopsy (SLNB) [22]. Nerve damage can be a reason for postoperative pain, motor defects and paresthesia. According to recent studies, surgical site infections were noted in 1.4% to 6.2% patients after breast surgery [23]. Wound infection and necrosis of mastectomy flaps can affect negatively wound healing [24]. Surgical debridement and skin grafting are necessary for some cases.

Among women who underwent breast surgery, chronic hypertension, high body mass index (BMI), cancer type, and evidence of metastasis were noted as the most significant risk factors for VTE, while type of breast surgery, type of axilla surgery, type of plastic surgery did not increase risk of VTE [25]. Also, hospital length of stay >3 days, and general anesthesia were noted as risk factors of developing VTE in patients undergoing reconstructive BC surgery [26]. As described, VTE may be a serious perioperative adverse event in patients treated with tamoxifen [27]. Therefore, administration of tamoxifen should be discontinued in a peri-operative period in some groups of patients. Time of discontinuation depends on thrombotic risk which is evaluated based on age, family history of VTE, BMI,
comorbidities, prosthetic valve, taking anticoagulation or active cancer. Patients with a very high risk of thromboembolism should be consulted by haematologist, while those with low thrombotic risk can receive the drug without stopping.

In the systematic review and meta-analysis, Saldanha et al. assessed breast reconstruction methods in women after mastectomy for BC or BC prophylaxis. They reported conducting autologous reconstruction (AR) is associated with higher risk of deep vein thrombosis or pulmonary embolism, while implant-based reconstruction (IBR) is related with a greater risk of reconstructive failure in the long term – 1.5 to 4 years and probably results in higher risk of breast seroma [28]. Surgeon therapy is related with decreased psychosocial well-being. Breast reconstruction is an opportunity for some patients to rebuild their breasts and increases their self-confidence. Prepectoral and total submuscular plane of implant may be associated with similar risks of infections [28]. Furthermore, human acellular dermal matrice (ADM) use during IBR probably increases the risk of implant failure/loss or need for explant surgery and may increase the risk of infections.

Radiation therapy

Ionizing radiation disrupts mitosis of epidermic cells leading to worse integrity of the skin [29]. Radiodermatitis [RD] is one of the most common complications during radiation therapy for cancers including BC [30]. According to Camidge et al., radiation recall dermatitis should be reported when the systemic therapy is administered at least 7 days after the end of radiotherapy, while radiosensitization is associated with radiosensitizers administered before or during radiation [31, 32]. RD manifests as erythema, pigmented changes, ulceration, itching, soreness, or peeling skin [33]. Moreover, RD can lead to dose reduction or interruption therapy, but also esthetic, psychological problems and affect negatively the daily functioning and quality of life [29, 30]. Developing RD is more probable among obese, older patients, females, and smokers [30]. In addition, drinking, sun exposure, other taken drugs play a role in dermatitis. Identifying risk factors of RD, early prediction of skin reaction, and early management is a way to improve the comfort of patients and prevention of deeper skin injuries [29]. Feng et al. proved data encapsulation screening and multi-region dose-gradient-based radiomics techniques have potential to be used in the prediction of skin toxicity induced by radiation in BC patients [29].

In case of chronic ulceration in the chest wall, the healing process is slow due to disturbed blood flow and cell regeneration after radiation [34]. Moreover, ulcers and granuloma formations can occur years after implant surgery [35]. Liu et al. in the meta-analysis and systematic review claimed that efficacy rates and toxicity were similar between conventional fractioned radiotherapy and hypofractionated radiotherapy in postmastectomy breast cancer [36]. Other toxic complications were radiation pneumonitis, skin symptoms or lymphedema.

Vieira et al. assessed risk factors of RD in females undergoing hypofractionated radiotherapy – the study revealed patients with large breasts and statin users were more prone to RD [33]. In contrast, skin color was considered a risk-reducing factor. It was noted that erythema – the most common symptom of RD during hypofractionated radiotherapy was mostly in the axillary region, while dry desquamation in the frontal region and moist desquamation in the inframammary fold region [33].

In prevention of RD, it is recommended to wash with warm water and mild soap, without skin irritation. Topical pharmacetics are glucocorticoids, vaseline ointment, olive oil, and ascorbic acid [30]. According to studies, cleaning reduces the severity of some skin symptoms but does not decrease the risk of RD incidence, while topical glucocorticosteroids are characterized by the potential to decrease the risk of severe dermatitis associated with
radiation therapy. Antibiotics use should be considered in case of infection suspension [32]. Recently, Yu et al. noted that Topical Chinese herbal medicine – TCHM has properties useful in the prevention and management of RD [30]. As described, proper skin care, use of mobile applications during BC therapy is helpful in the prevention of skin adverse effects of therapy [33].

RD was also noted in early-breast cancer after the addition of regional nodal irradiation following mastectomy. Although it improved disease-free survival rate it increased incidence of other side effects – pneumonitis and delayed events such as lymphedema, telangiectasia of the skin, and subcutaneous fibrosis [37]. For reducing radiation exposure to the chest, heart and lungs, it is worth considering prone positioning, respiratory control, or intensity-modulated radiotherapy [38].

Chemotherapy

Adjuvant chemotherapy is associated with improvements in outcomes, but also with long-term complications. The early toxicities – 0–6 months of adjuvant treatment include fatigue, alopecia, cytopenia, muscle pain, neurocognitive dysfunction, and chemo-induced peripheral neuropathy, while late side effects – after 6 months of treatment involve cardiomyopathy, second cancers, early menopause, sterility, and psychosocial impacts [2].

Febrile neutropenia is common and potentially lethal toxicity of chemotherapy [39]. In the study of Nomura et al., they noted association between chemotherapy-induced febrile neutropenia and the hormone receptor-negative/HER2-positive subtype in Japanese patients [39]. In the II phase study conducted on women with large operable or locally advanced carcinoma of the breast, combination of docetaxel and epirubicin led to diarrhea in more than 25% of patients and grade 4 neutropenia in 80% of patients [40].

Use of chemotherapeutics in metastatic cancer is associated with lots of adverse events, which can be unspecific or specific for some type of drugs. It is well known that anthracyclines are cardiotoxic agents [2]. Doxorubicin is associated with heart damage, myelosuppression, hypersensitivity, extravasation [41]. Combination therapy comprising doxorubicin and cyclophosphamide led to myelotoxicity, cardiotoxicity, hepatic or renal dysfunction. Clinical studies suggested conjugation nanoparticles to doxorubicin could be a chance for less toxicity in the therapy of advanced BC [42]. The next group of chemotherapeutics – taxanes is associated with neurotoxicity [2]. One of them – paclitaxel leads to neuropathy, myelosuppression, hypersensitivity, extravasation, while toxicities of paclitaxel with gemcitabine were neutropenia, fatigue and neuropathy [43]. Therefore, patients with neutropathies should avoid antimicrotubule agents. Chemotherapy in BC patients also affects cognitive functions and quality of life [44]. Cognitive training and physical activity can be used as methods to manage cognitive changes.

Administration of oral capecitabine contributes to edema, fatigue, diarrhea, hypersensitivity, cardiotoxicity. In the study assessing efficacy of adjuvant capecitabine for BC after preoperative chemotherapy, the most common adverse effect was the hand-foot syndrome [45]. In the next study, Hoon et al. evaluated use of chemotherapy regimens containing capecitabine compared with regimens not containing capecitabine on receptor-positive and hormone receptor-negative BC cases [46]. Addition of capecitabine as neoadjuvant and adjuvant therapy resulted in higher frequency of diarrhea and hand-foot syndrome. In addition, 3 or 4 grade febrile neutropenia was less common in capecitabine arms in adjuvant studies, while there were no differences in neoadjuvant settings. Hand-foot syndrome manifests in redness, tightness of the skin, palmoplantar numbness, pain in the soles and palms [46, 47]. Moreover, in recent studies hand-foot syndrome was noted as a predictor of prolonged progression-free survival (PFS) and overall survival (OS) in patients
treated with bevacizumab plus capecitabine (BEV-CAP) for locally recurrent/metastatic BC (LR/mBC) [48].

Some chemotherapeutics – particularly taxanes and CMF – cyclophosphamid, methotrexate, 5-fluorouracil and age are risk factors of cessation of menses [49]. The group of younger than 35 years old patients have quite high potential to recover menses, in contrast to most older than 40 age. Cessation of menstrual cycles affects quality of life and is associated with a variety of unpleasant symptoms such as hot flashes, headaches, vaginal dryness and other genitouterinal symptoms.

Furthermore, recent studies suggest that chemotherapy may promote resistance of cancer cells what contributes to worse therapeutic effects [50]. Chemoresistance can be caused by drug inactivation, overexpression of the ATP-binding cassette (ABC) transporters, dysregulation of apoptosis, and cancer stem cells [50]. Chemosensitivity and chemoresistance assays, gene expression profiles and positron emission tomography assays are methods useful in prediction of resistance to chemotherapeutic agents. Moreover, nanoparticles including liposomes, polymeric nanoparticles or polymeric micelles have potential to reduce the toxicity and overcome the chemoresistance of conventional chemotherapy [51]. The mechanism of nanomedicines is based on passive targeting, active targeting and stimuli responsive tumor targeting of nanocarriers to tumor cells.

**Targeted therapy**

Administration of anti-HER2 drugs such as trastuzumab may lead to cardiac dysfunction [6]. Moreover, prior use of anthracyclines with older age and hypertension is suggested to increase the risk of cardiotoxicity. In the 3 phase study with patients with HER2+ advanced BC, cardiac dysfunction was observed among 27% of patients on combination therapy – trastuzumab and chemotherapy, and 8% of patients receiving chemotherapy alone [52]. Radiotherapy is the next factor with potential to increase risk for cardiotoxicity [6]. According to guideline recommendations for trastuzumab, cardiac function monitoring should be started before starting the therapy, during the course, and 2 years after last dose of the drug in adjuvant therapy [6]. If left ventricular ejection fraction – LVEF decrease is observed, interruption of the therapy should be considered. Interestingly, other anti-HER2 agents – lapatinib, trastuzumab emtansine – T-DM1, pertuzumab are associated with a lower risk of cardiotoxicity.

**Endocrine therapy**

As a consequence of endocrine therapy, patients are affected by vasomotor, musculoskeletal, and vulvovaginal symptoms [53]. Hot flashes are noted in 80% of patients receiving tamoxifen [54]. Due to agonistic estrogen activity, tamoxifen can contribute to endometrium neoplasm, uterine sarcoma and increase the thromboembolic risk [8]. Furthermore, the most commonly reported pathological finding in the uterus among postmenopause women with BC receiving tamoxifen, are endometrial polyps [55]. These abnormalities have the potential to transform into malignant neoplasms, so it is necessary to ensure surveillance in patients treated with tamoxifen and consider removal of them.

In a meta-analysis, Yu et al. noted insignificantly higher risk of venous thromboembolism in patients with BC treated with tamoxifen compared to aromatase inhibitors [56]. Additionally, the use of aromatase inhibitors was associated with a higher risk of stroke, angina, myocardial infarction, and heart failure, compared to tamoxifen. Interestingly, in the study assessing cardiotoxicity in patients after menopause with BC, consuming adjuvant aromatase inhibitors or tamoxifen, they noted that tamoxifen can have cardioprotective properties [57]. In the next study, conducted on postmenopausal women
with hormone receptor-positive BC, thromboembolic events and cardiac effects such as hypertension, cardiac insufficiency, and supraventricular arrhythmia were observed more frequently in the letrozol group than in tamoxifen arm [58]. Instead, there was no difference in frequency of myocardial infarction and cerebrovascular events osteopenia/osteoporosis, fracture rate between letrozol and tamoxifen. Furthermore, in the study involving premenopausal BC patients treated with tamoxifen alone, tamoxifen plus ovarian suppression, or exemestane – aromatase inhibitor plus ovarian suppression, occurrence of adverse effects was higher in the groups combined with ovarian suppression [59]. Patients after bilateral oophorectomy without estrogen replacement were characterised by higher risk of depression, diabetes or osteoporosis [59]. However, longer use of tamoxifen as BC treatment increases the risk of tooth loss [60]. Other adverse effects of tamoxifen and its metabolites are nausea, nasopharyngitis, respiratory infections, increased lacrimation, diarrhoea, myalgia [61]. Interestingly, nausea was more frequent in women receiving trastuzumab who are ER positive/also receiving hormone therapy, compared to group of women who are ER negative/not receiving hormone therapy [61].

Both tamoxifen and letrozol can be associated with elevated liver enzymes – therapy using them requires regular monitoring liver enzymes [62]. Use of tamoxifen during BC therapy by women with the A2 allele of CYP17A1 increases risk of hepatic steatosis, but the exact mechanism of toxicity remains unclear. In addition, the use of diagnostic imaging methods can not be enough to distinguish between changes – cancer metastases and steatosis [62]. Therefore, liver biopsy may be considered among some patients. In the study evaluating adverse events of tamoxifen among male patients, the most common side effects were gastrointestinal, and cardiovascular events while psychiatric disorders were more frequently reported in males with BC [63].

**Immune checkpoint inhibitors**

Immune checkpoint blockade has emerged as a successful therapy in many malignant tumors, while its use in BC treatment is in development [13]. However, due to mechanism of action, it increases risk of adverse effects called immune-related adverse events (irAEs) [64]. Toxicities of ICIs have features, which distinguish them from conventional chemotherapy-induced adverse effects. irAEs can affect any organ – usually immune-related therapy, or after treatment [65].

Generally, the common irAEs in patients with BC are rash and infusion reaction [64]. Other irAEs manifested as increased aspartate aminotransferase, cough, endocrine disorders – dysfunction of thyroid gland and adrenal insufficiency. Moreover, use of PD-1 or PD-L1 inhibitors in TNBC results in serious irAEs very rarely (<1%), except for adrenal insufficiency (1.70%) [67]. However, the frequency of serious irAEs is higher in PD-(L)1 inhibitors than chemotherapy as monotherapy. Other non-serious irAEs such as aspartate aminotransferase (AST) elevation, hypothyroidism, pruritus, rash and fever are noted more frequently in PD-(L)1 arm than chemotherapy. According to meta-analysis, atezolizumab combined with nab-paclitaxel was related with a higher incidence of serious adverse events, dermatological, endocrine, neurological adverse effects compared with chemotherapy alone [68].

Severity of irAEs is classified according to the Common Terminology Criteria for Adverse Events (CTCAE) grading system [69]. When grade 1 events occur, ICIs therapy may be continued [70]. For grade 2-4 irAEs, it is recommended usually to withhold immunotherapy. ICIs may resume when adverse events resolve, but permanent discontinuation is sometimes necessary. The management of irAEs is based on
immunosuppressants – specified with infections and toxicity to lung or liver [71]. Moreover, high-dose corticosteroid administration can contribute to reduced efficacy of ICIs. Similarly to other therapeutic methods, drug resistance is a challenge in immunotherapy.

**Summary**

Breast cancer treatment requires a multiprofessional approach with surgery, radiotherapy, and systemic therapies. However, each therapeutic option is associated with adverse effects, which can limit treatment efficacy, and lead to prolonged recovery, and patient discomfort. A variety of toxicities is associated with an impact on patient’s quality of life. Furthermore, patients should be informed of potential adverse effects associated with therapeutic method which is used. It allows for early detection and effective treatment. As we identify patients at greater risk for adverse events of breast cancer therapy, it is vital to choose more individualised, targeted and tolerable treatment.

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