Review article

How to deal with the side effects of long-term pharmacotherapy with aromatase inhibitors?

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ABSTRACT

Aromatase inhibitors are effective drugs used in adjuvant therapy of breast cancer. Their action is to reduce the level of oestrogens produced in adipose tissue in women in physiological or pharmacologically induced menopause. Nevertheless, long-term pharmacotherapy with aromatase inhibitors may lead to various side effects that may significantly affect the quality of life of patients. The following article presents the most common problems associated with aromatase inhibitor therapy and describes how to deal with these undesirable side effects.

Key words: breast cancer, adverse events, safety of treatment

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INTRODUCTION

Breast cancer is still the most frequently cancer diagnosed in women [1]. Despite the constant increase in incidence, improvement in survival rates for this cancer is observed. Therefore, more and more attention is paid to maintaining or improving the quality of life of patients and introducing methods of dealing with the side effects of treatment [2, 3].

This is particularly important in the case of long-term hormone therapy, which is recommended for patients diagnosed with hormone-dependent cancer. It is believed that this biological subtype is diagnosed in approximately 75–80% of cases [4]. Aromatase inhibitors (AI) have been shown to be more effective than the selective oestrogen receptor modulator (SERM), tamoxifen, both in neoadjuvant, adjuvant and metastatic breast cancer treatment [5, 6].

AI are used as an adjuvant therapy in hormone-dependent breast cancer according to the guidelines of the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) [7, 8]. According to the recommendations, AI are used longer, and the constant lack of oestrogen may affect a number of physiological functions, which leads to a deterioration of the quality of life of patients [6, 9]. Some patients may even decide to resign from continuing therapy, if they do not receive adequate support from an oncologist and information about the possibilities of reducing the disturbing symptoms. In such a case, the effectiveness of adjuvant treatment will be lower and a significant number of patients may experience a recurrence of cancer [10].

In randomized clinical trials, the rate of premature discontinuation of aromatase inhibitors was 8–24% [10]. However, treatment discontinuation rates in daily clinical practice ranged from 31% to 73%, suggesting that there may be important differences in how adjuvant treatment is delivered [10].

AROMATASE INHIBITORS IN THE ADJUVANT TREATMENT OF BREAST CANCER

AI are undoubtedly an effective treatment for breast cancer in women in the postmenopausal period. Their action is to reduce the level of oestrogens produced in adipose tissue. Nevertheless, long-term AI pharmacotherapy may lead to various side effects that may significantly affect the quality of life of the patients. Two types of AI are available: the steroidal irreversible aromatase inactivator (exemestane) and the nonsteroidal reversible inhibitors (anastrozole and letrozole). A randomized phase III trial in 4,136 postmenopausal patients with hormone receptor-positive, node-positive early-stage breast cancer showed that letrozole was non-inferior to anastrozole in terms of disease-free survival, overall survival, and treatment safety. However, the trial was terminated prematurely due to shorter than expected disease-free survival [5]. A recently published meta-analysis showed similar effectiveness of all three AI [11]. However, the data comparing quality of life and treatment tolerability is limited.

It is believed that the incidence of skeletal side effects may be lower for exemestane than for the other two AI, but information on this subject is quite limited [5].

The most frequently described side effects of AI include vasomotor symptoms, muscle and joint pain, fatigue, hair thinning, and depression. However, bone loss is usually considered the most important [2, 3, 5].

The state of oestradiol deficiency causes increased bone remodelling and negative bone balance. This leads to loss of bone tissue, deterioration of the microstructure and bone fragility, predisposing to fractures. Fractures, in turn, are associated with increased morbidity, mortality and high socioeconomic burden [5].

Over recent years, many publications have appeared to provide guidance on how to effectively prevent and control AI-related adverse events.

VASOMOTOR SYMPTOMS

Approximately 95% patients receiving adjuvant hormone therapy experience vasomotor symptoms. Although often ignored by medical staff, they cause anxiety for patients and are the most common reason for discontinuing hormone therapy [12]. Vasomotor symptoms are more frequently observed in patients receiving both goserelin and AI than in patients receiving AI alone. Vasomotor symptoms result from the altered function of the thermoregulatory centre contained in the hypothalamus, caused by hypoestrogenism [13] and are regulated by several neurotransmitters, mainly serotonin and norepinephrine [13]. Selective serotonin reuptake inhibitors (SSRIs) and norepinephrine reuptake inhibitors (SNRIs) may alleviate vasomotor symptoms [3, 13]. In particular, venlafaxine (SNRI) showed a reduction in the incidence of hot flashes in as many as 37–61% of patients (37.5 mg/24 h).

Anticonvulsants such as gabapentin and pregabalin showed similar effectiveness in reducing the incidence of vasomotor

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symptoms, but had a poorer tolerability profile. Additionally, many patients benefit from non-pharmacological interventions, including acupuncture, cognitive-behavioural therapy (CBT) and physical activity.

MUSCLE AND JOINT PAIN

Nearly 50% of patients receiving AI experience joint and muscle pain [14]. Administering another AI may be a helpful treatment option for patients suffering from joint pain. Duloxetine (SNRI) could be considered among potential pharmacological interventions. In patients with AI-related arthralgia, treatment with duloxetine led to a reduction in symptoms in approximately half of the patients [15].

Regarding other pharmacological interventions, a study on the effect of high-dose vitamin D supplementation was recently published and showed no significant effect on AI-related joint pain [16]. Glucosamine and chondroitin sulphate have also been evaluated in this context and have shown significant improvements in the incidence and severity of joint pain in more than half of patients [17]. In the prospective phase II study, where a combination of furosemide 20 mg and spironolactone 50 mg every other day was administered, as many as 84% of patients treated with AI showed a significant reduction in pain and joint stiffness, with improvement noticeable already in the first week of treatment [18].

The role of bisphosphonates in this respect was also assessed, and a lower incidence of joint pain was found when zoledronic acid was administered every 6 months at the end of the first year of treatment [3].

It has also been shown that aerobic exercise can reduce musculoskeletal pain. Additionally, acupuncture has shown long-term beneficial effects on AI-related pain.

METABOLIC DISORDERS

Oestrogen deficiency is a key contributor to the development of metabolic disorders, including weight gain, diabetes, dyslipidaemia and non-alcoholic fatty liver disease (NAFLD). Approximately 21% of patients receiving AI have reported weight gain [19]. In subsequent stages, hypoestrogenism may lead to insulin resistance and increase the risk of type II diabetes [3]. NAFLD was observed in more than ⅓ of patients receiving AI treatment, likely due to an increased risk of dyslipidaemia [3].

Several studies have assessed the effectiveness of lifestyle interventions (including physical exercise and a healthy diet), in reducing the risk of metabolic disorders associated with hormone therapy. Weight loss and physical activity have been shown to reduce levels of pro-inflammatory cytokines and markers that are associated with breast cancer recurrence and metabolic comorbidities [3].

So far, pharmacological interventions (naltrexone, bupropion) have not been shown to be more effective in the treatment and/or prevention of metabolic disorders in patients receiving AI compared to interventions based only on lifestyle changes [20].

OCULAR TOXICITY

The use of AI may lead to the dry eye syndrome due to the absence of the protective effect of oestrogens on the ocular surface [3]. This condition affects about 30% of patients.

It has been shown that androgen-based eye drops can improve the dry eye symptoms in up to 30% of patients [21].

INSOMNIA

More than half of patients receiving adjuvant hormone therapy experience sleep disturbances, which may have a detrimental effect on their daily functioning and lead to mood disorders, concentration disorders and difficulties in focusing attention [3].

Pharmacological interventions (e.g. benzodiazepines) are usually recommended. However, the non-pharmacological approach (sleeping in a dark environment and using stress-reducing activities) is of fundamental importance.

Physical activity has also a positive impact on sleep. Acupuncture is an additional option that has been shown to be effective in reducing sleep disorders [22].

FATIGUE

Fatigue is a common complaint among patients receiving AI, reported by over 80% of patients [3]. Despite the frequent occurrence of this symptom, data regarding the available intervention methods in this area is very limited. Fatigue is known to be associated with a sedentary lifestyle and obesity, so physical activity and a healthy diet are recommended. It has been reported that yoga or acupuncture can alleviate symptoms of fatigue [22].

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ALOPECIA

Alopecia is observed in as many as 9% of patients receiving tamoxifen and 2.5% of patients receiving AI [23]. A slight increase in hair loss is usually observed and usually occurs within the first year of treatment. Although this is not a common symptom, it is estimated that as many as 8% of patients discontinue treatment due to hair loss.

A daily topical 5% minoxidil solution has been shown to alleviate the occurrence of alopecia in 80% of patients receiving hormone therapy [23].

GENITOURINARY SYNDROME OF MENOPAUSE

Hypoestrogenism occurring during menopause may lead to dysfunction of the vaginal epithelium and urinary tract, causing symptoms such as vaginal dryness, dyspareunia and painful urination. These symptoms occur together and are referred to as the genitourinary syndrome of menopause [24].

It is estimated that as many as 20% of patients receiving adjuvant hormone therapy discontinue treatment due to the occurrence of genitourinary syndrome of menopause [3].

Non-hormonal drugs should be administered as treatment. Vaginal suppositories with vitamin D, E showed an effect on the atrophy of the vaginal epithelium in patients receiving AI.

One can also use lidocaine vaginally, as well as lubricants and moisturizing agents.

Another potential option is intravaginal laser therapy, which can stimulate collagen synthesis and blood vessel formation [24].

In addition to physical symptoms, patients also complain of loss of libido and discomfort during a sexual intercourse. In such cases, cognitive-behavioural therapies are primarily recommended.

OSTEOPENIA

Adjuvant hormone therapy for breast cancer causes bone mass loss and deteriorates bone metabolism [3, 5]. AI reduce circulating oestrogen levels, thereby increasing bone turnover. The combination of goserelin and AI accelerates bone mass loss to a greater extent than the combination of goserelin and tamoxifen [5].

International guidelines recommend careful assessment of fracture risk in patients receiving adjuvant AI therapy by baseline densitometry.

Adopting a healthy lifestyle is also recommended, which should include quitting smoking, limiting alcohol consumption, taking up physical activity, planning meals rich in calcium and supplementing vitamin D [3]. If the risk of osteoporosis is identified, it is recommended to use antiresorptive drugs such as bisphosphonates (pyrophosphate analogues that accumulate in sites of bone remodelling) and denosumab (a monoclonal antibody that binds to the RANK receptor involved in osteoclast activation) [25]. It is worth noting that, in addition to their osteoprotective effects, antiresorptive agents may also have an impact on reducing the risk of bone metastases by modifying the bone microenvironment [3, 5].

CONCLUSION

AI and tamoxifen are currently the basis of adjuvant treatment of hormone-dependent breast cancer. Despite its proven effectiveness, many women are afraid of this treatment due to its side effects. Therefore, it is of utmost importance to manage potential side effects of the therapy in a proactive way. Additionally, new therapy options have appeared in the adjuvant treatment of breast cancer (olaparib, inhibitors of cyclin-dependent kinases 4 and 6) in recent years, which may pose additional challenges in the proper management of side effects.

Toxicity occurring during adjuvant hormone therapy is often underestimated, but it has a significant impact on the quality of life of patients and may negatively affect compliance with therapeutic recommendations, and thus worsen the results of the breast cancer treatment.

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