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LETTERS TO THE EDITOR

Leg cramps associated with tamoxifen use – possible mechanism and treatment recommendations

Dear Editor,

Since 1970s, tamoxifen has widely been used in the adjuvant and metastatic settings and also in risk reduction of hormone receptor positive breast cancer. Long-term use of tamoxifen in the adjuvant setting of hormone receptor positive breast cancer, such as up to 5 or 10 years duration, is standard of care and associated with favorable survival outcomes, almost in all stages of disease. Symptomatic side effects such as painful cramps due to tamoxifen are as important as adverse effects which might lead to treatment discontinuation. Today, we have been experiencing leg and foot cramps in our patients receiving tamoxifen in our clinic, this condition being severe enough to lead to treatment discontinuation with negative impact on the quality of life in breast cancer survivors.

Recurrent leg cramp associated with tamoxifen use is a common side effect and causes severe acute leg pain. However, the mechanism of this side effect remains obscure [1,2].

In the literature, there are several reports suggesting that estrogen increases blood flow in muscle tissue and vessels by releasing nitric oxide (NO) and producing direct vaso-myorelaxant effect. In a study, basal blood flow was found to be lower in estrogen-deficient postmenopausal women compared to premenopausal counterparts [3]. In two other studies, estrogen replacement therapy has been found to increase serum NO levels in postmenopausal women [4,5]. We favor the explanation that leg cramps, particularly developing in night sleep, may be triggered by reduced blood flow due to postural changes. Instead of using vitamin D or magnesium tablets which have been mostly used for these cramps and failed to show efficience, systemic or local treatments (e.g. sildenafil, nitrates, pentoxyfylline etc) which increase NO levels may be useful and may improve the symptoms. Our hypothesis on this issue should be supported with relevant trials.

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When should we give aromatase inhibitors for insomnia; early in the day or after dinner?

Dear Editor,

Insomnia is a sleep disorder characterized by difficulty in falling asleep, remaining asleep or waking up too early despite inadequate time to sleep. Insomnia is a condition that lasts at least 3 times per week for 3 months and is a major societal health problem . Patients with insomnia have fatigue, poor concentration, mood disturbance and daytime sleepiness . Some medical conditions are associated to insomnia such as major depression, chronic pain, pulmonary disease, cancer and heart failure. Major depressions are particularly common in patients with insomnia. Also sympathetic activation increases with insomnia as a result of increased incidence of hypertension and cardiac failure. Insomnia may also be secondary to acute stress or medication.

Insomnia is more common in breast cancer patients compared to patients with other cancer types. This may be not only due to the psychological trauma of cancer diagnosis but also to medication. Hormonal drugs (tamoxifen and aromatase inhibitors/AI) often induce menopause and menopausal symptoms which include hot flashes. AI are used in estrogen positive postmenopausal breast cancer patients and are proven to improve survival by blocking the conversion of androgens to estrogens. AI have some side effects such as bone loss, arthralgia, vaginal dryness and hot flashes and can also cause insomnia. In a questionnaire study, insomnia was identified in 17% of patients with breast cancer [1]. Desai et al. evaluated the prevalence and risk factors for insomnia among breast cancer patients on AI [2]. Indeed insomnia complaints were found to exceed 50% of breast cancer patients who were prescribed AI as adjuvant treatment.They also demonstrated that clinically significant insomnia was highly associated with joint pain, hot flashes, anxiety and depression, as well as age and time since diagnosis. In this study, insomnia was observed to be more frequent among patients younger than 55 years of age compared to those older than 65 years. Also, insomnia was more frequent among patients who were within 2 to 5 years after diagnosis than those within the first 2 years after onset. Another trial (Tamoxifen Exemestane Adjuvant Multinational/TEAM) has investigated the quality of life in relation to tamoxifen or exemestane treatment in postmenopausal breast cancer patients [3]. In this study, it was found that exemestane-treated patients reported more insomnia than tamoxifen-treated patients. Half time of anastrozole and letrozole is about 48 hrs and it mainly happens (85%) via hepatic metabolism. Exemestane is rapidly absorbed after meals and time to peak plasma concentration is 1.2 hrs. Time to peak plasma concentration of anastrozole is about 2 hrs without food and 5 hrs with food [4].

We do therefore recommend to give AI early in the day to patients with insomnia.

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Which situations require attention during radiotherapy in patients with Behcet's disease-associated malignancy?

Dear Editor,

Behcet's disease (BD) is a multisystemic vasculitis which is characterized by exacerbations and remissions of ocular inflammation, oral and genital ulcers, cutaneous lesions, as well as neurological and vascular symptoms. It is an endemic disease to countries such as Turkey, Iraq, Iran, Korea and Japan which are alongside the ancient Silk Road [1,2].

Although significant improvements have been made in understanding the etiopathogenesis of BD compared to previous years, this entity is still unclear. The core of the very hypothesis is that it is a disease which is a combination of infectious agents, immune disorders, environmental and genetic factors [2,3].

Although there are many publications related to BD, only a limited number of publications exists which compile cases of cancer associated with BD due to its rare occurrence. It is known that risk of malignancy is increased in many connective tissue diseases and vasculitis, but this situation is rare in BD [3,4].

The incidence of solid tumor occurrence in patients with BD was reported to be the same as the incidence of cancer in the general population [4,5]. The underlying cause for development of cancer in BD is thought to be caused by vasculitis of small blood vessels and autoimmune disorders. In BD, changes were shown not only in cellular immunity but also in humoral immunity. This was thought to predispose to cancer development. It was also emphasized that drugs which are used in the treatment of BD promote carcinogenesis.

Cengiz et al. followed up 400 patients with BD for about 10 years and they reported malignancy in 13 patients [2]. In another study, Kural and colleagues followed up 387 patients for 20 years and malignancy was reported in 8 patients [3]. Both of these studies showed that the incidence of cancer in BD was the same as the incidence of cancer seen in the general population [2,3]. In Korea, in a study on 506 patients, morbidity due to cancer in patients with BD was lower compared with the general population [4]. Cengiz et al. reported that in cancer patients with BD, both surgery and chemotherapy were quite reliable; in case of radiation therapy, severe late toxicity could be seen [1,2].

Publications about BD-associated malignancy cases that evaluated radiation therapy for acute and chronic side effects are mostly at the level of case report [1,5]. Radiotherapy is planned for these patients according to feedbacks and experiences in the literature due to lack of publications about follow up and treatment of these patients.

Because BD is a vasculitis, there may be an increase in radiotherapy-related side effects. Moreover, especially during exacerbations, radiation treatment should be closely monitored for acute and chronic toxicity. Furthermore, during radiotherapy, it should be considered whether drugs used for BD treatment could increase morbidity. Multicenter collaboration which should provide follow up and treatment roadmap is needed in BD-associated cancer cases.

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