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COVID-19 infection can cause chemotherapy resistance development in patients with breast cancer and tamoxifen may cause susceptibility to COVID-19 infection

ABSTRACT

Breast cancer is the most common cancer in women and is the second most common cause of death in women. Estrogen plays an important role in breast tumor etiopathogenesis. Tamoxifen and other anti-estrogen drugs are used in breast cancer patients who have a positive estrogen receptor (ER). While angiotensin II plays a key role in breast cancer etiology and causes tamoxifen resistance, angiotensin 1–7 has been reported to may reduce the spread and invasion of breast cancer. During the COVID-19 infection, the virus blocks ACE2, and angiotensin 1–7 production discontinued. Angiotensin III production may increase as angiotensin II destruction is reduced. Thus, aminopeptidase upregulation may occur. Increased aminopeptidase may develop resistance to chemotherapy in breast cancer patients receiving chemotherapy. Estrogen can have a protective effect against COVID-19. Estrogen increase causes ER-α upregulation in T lymphocytes. Thus, estrogen increases the release of interferon I and III from T lymphocytes. Increasing interferon I and III alleviates COVID-19 infection. Tamoxifen treatment causes down-regulation, mutation, or loss in estrogen receptors. In the long-term use of tamoxifen, its effects on estrogen receptors can be permanent. Thus, since estrogen receptors are damaged or downregulated, estrogen may not act by binding to these receptors. Tamoxifen is a P-glycoprotein inhibitor, independent of its effect on estrogen receptors. It suppresses T cell functions and interferon release. We think tamoxifen may increase the COVID-19 risk due to its antiestrogen and P-glycoprotein inhibitory effects.

Dear Sir,

Despite all serious precautions, the novel coronavirus disease 2019 (COVID-19) outbreak is spreading rapidly worldwide. The virus is more common in patients with comorbid conditions such as hypertension, diabetes mellitus, and cancer, and is more fatal in these patients. The immune system of cancer patients is weak due to reasons such as chemotherapy and radiotherapy treatments, and these patients are more susceptible to infections. We determined that the frequency of COVID-19 infection is more common in patients with breast cancer than other types of cancer. The COVID-19 infection was diagnosed by detecting the viral RNA by real-time reverse transcription-polymerase chain reaction (RT-PCR) using throat and nasopharyngeal swabs which were taken from patients with fever, dry cough, weakness, and shortness of breath. We performed a chest computed tomography on patients with a positive RT-PCR test and diagnosed patients with COVID-19 pneumonia according to the current guideline [1]. All of our patients with breast cancer had a history of tamoxifen use. Two patients were actively using tamoxifen, others 6 patients had a history of using tamoxifen. The average age of these patients was 54.5 ± 5.3 years, and 3 of them had severe viral pneumonia. None of our breast cancer patients had comorbid diseases. According to our observation, the use of tamoxifen increases the susceptibility to COVID-19 infection in breast cancer patients. We speculate that estrogen plays a protective role against COVID-19 infection and tamoxifen increases the risk of COVID-19 in breast cancer patients. Therefore, patients with breast cancer can be susceptible to COVID-19 infection.

Breast cancer is the most common cancer in women and is the second most common cause of death in women. Estrogen plays an important role in breast tumor etiopathogenesis. Tamoxifen and other anti-estrogen drugs are used in breast cancer patients who have a positive estrogen receptor (ER). There is a strong relationship between both breast cancer etiopathogenesis and tamoxifen resistance with the renin-angiotensin system (RAS). Angiotensin-converting enzyme (ACE) upregulation has been detected in some breast cancer types [2]. ACE converts angiotensin I to angiotensin II. Angiotensin II binds to AT1 receptors, then stimulating many pro-angiogenic factors and it is responsible for the proliferation and angiogenesis of breast cancer [2]. Angiotensin II converted to Angiotensin III by aminopeptidase. Angiotensin III is associated with angiogenesis and tumorigenesis. Aminopeptidase upregulation is closely related to breast cancer. Aminopeptidase stimulates tumorigenesis and can lead to the development of breast cancer [3]. ACE2 converts angiotensin II to angiotensin 1–7 which is an anti-inflammatory antioxidant and vasodilator. Angiotensin 1–7 has antiproliferative and anticancer effects [2]. While angiotensin II plays a key role in breast cancer etiology and causes tamoxifen resistance, angiotensin 1–7 has been reported to may reduce the spread and invasion of breast cancer. During the COVID-19 infection, the virus blocks ACE2, and angiotensin 1–7 production discontinued. Angiotensin III production may increase as angiotensin II degradation is reduced. Thus, aminopeptidase upregulation may occur. Breast cancer patients using active tamoxifen may develop tamoxifen resistance due to RAS and aminopeptidase activation [3]. Also, increased aminopeptidase may develop resistance to chemotherapy in breast cancer patients receiving chemotherapy.

COVID-19 has a close relationship with the RAS system. The virus enters the cell by binding to ACE2 at acidic pH and settles into the cytosol. ACE2 upregulation increases the viral load [4] ACE2 level of premenopausal women is higher than postmenopausal women and men [5]; however, COVID-19 infection is severe in men and postmenopausal women [5]. Estrogen can have a protective effect against COVID-19. It has been reported that angiotensin 1–7 may have a protective effect against ischemic cardiac damage and acute respiratory distress syndrome. In an animal experiment, long-term angiotensin 1–7 infusion was found to have strong antioxidant and vasodilating effects in female rats; however, there was no positive effect of long-term angiotensin 1–7

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infusion in male rats [5]. Presumably, estrogen may reinforce the vasodilator and antioxidant effect of angiotensin 1–7. Besides, estrogen increase causes ER-α upregulation in T lymphocytes. Thus, estrogen increases the release of interferon I and III from T lymphocytes. Increasing interferon I and III alleviates COVID-19 infection [6]. Therefore, the idea has been claimed that exogenous estrogen therapy may be beneficial in COVID-19.

Tamoxifen, a selective estrogen receptor antagonist, has an antiestrogenic effect on breast tissue, while it shows the estrogenic effect on endometrium and bone. Tamoxifen is used to treatearly or advanced-stage breast cancer which has positive estrogen receptors. Tamoxifen treatment causes down-regulation, mutation, or loss in estrogen receptors [7]. In the long-term use of tamoxifen, its effects on estrogen receptors can be permanent. This effect of tamoxifen is on breast tissue; however, its effect may not be limited to breast tissue alone. There is plenty of ER in the lung tissue [8]. It has been reported that tamoxifen may have an apoptotic effect on ER receptors in the lung tissue [9]. Thus, since estrogen receptors are damaged or downregulated, estrogen may not act by binding to these receptors. Tamoxifen is a P-glycoprotein inhibitor, independent of its effect on estrogen receptors [10]. It suppresses T cell functions and interferon release. We think tamoxifen may increase the risk of COVID-19 due to its antiestrogen and P-glycoprotein inhibitory effects. The frequency of COVID-19 and the relationship between tamoxifen and COVID-19 in breast cancer patients should be demonstrated by studies.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2020.110091.

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