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LETTER TO THE EDITOR

Tamoxifen in breast cancer survivors with COVID 19: stop or go?

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The COVID 19 pandemic threatens human health in many ways. Although vaccines that have completed phase 3 trials are being used today, it is estimated that the risk of infection will continue for a while. Many people will continue to suffer from severe COVID 19 disease in this process, and some of these patients will unfortunately die. The most common known cause of death in COVID 19 infection is acute respiratory distress syndrome (ARDS) [1]. It is known that advanced age, obesity, chronic diseases such as diabetes mellitus, hypertension increase the mortality of COVID 19 [1]. There is also evidence that COVID 19 infection is more fatal in patients with cancer. We experienced an increased risk of venous thromboembolism (VTE) in viral infections in the H1N1 pandemic (5.9%). However, in COVID 19 infection, compared to H1N1, VTE was found much more frequently (15–45%) [1]. Although it is not known precisely by which mechanism the risk of VTE increases in COVID 19, it is thought that increased systemic inflammation and endothelial damage have an essential role in this issue [1]. The risk of VTE is increased not only in hospitalized patients but also in outpatient COVID 19 cases. A meta-analysis showed that among patients with COVID 19, the mortality risk was significantly increased in patients with VTE compared to those without (OR 1.74; 95% CI 1.01–2.98) [1]. Several groups recommended low molecular weight heparin (LMWH) for every COVID patient if there are no contraindications, but there is no clear consensus on this issue.

Endocrine therapy is the cornerstone of adjuvant therapy in hormone-positive breast cancer. Tamoxifen, a selective estrogen receptor modulator (SERM), is used as an adjuvant endocrine treatment, especially in premenopausal patients, in many centers worldwide. Venous thromboembolism is one of the important side effects of Tamoxifen. Estrogen increases the risk of thrombosis by decreasing antithrombin III and protein S in the blood. Tamoxifen, which also has an estrogen partial agonist effect, is thought to cause thrombosis with this mechanism [2]. Although 4–5% of tamoxifen users have VTE, it has been shown that these rates increase significantly in the use of Tamoxifen for more than 5 years. VTE's risk increases in those with additional risk factors such as obesity, thrombophilia, smoking, and major surgery [2]. There are suggestions that the patient's treatment using tamoxifen, who is planned to have major surgery, should be interrupted for 2–3 weeks [2]. But there is no guideline information on the subject.

COVID 19 infection and Tamoxifen appear to be independent risk factors for VTE. Does a COVID 19 infection in a patient on Tamoxifen increase the risk of VTE—or vice versa? We know from studies that the combination of independent VTE risk factors increases VTE's risk much more. This suggests that the combination of COVID 19 infection and Tamoxifen may increase the risk of VTE. So what should we do if a patient with breast cancer using adjuvant Tamoxifen gets COVID 19 infection?

- Should we stop Tamoxifen?
- If Tamoxifen is to be discontinued, should we stop for 2–3 weeks as recommended in the perioperative period?
- Or should we continue Tamoxifen with LMWH?

In a case report, hyperacute multiorgan thromboembolism was observed in a patient with COVID 19 who was using Tamoxifen despite anticoagulant treatment. Stopping Tamoxifen for at least 2 weeks or much more (due to the accumulation of tamoxifen in adipose tissue in the long

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term) may prevent fatal consequences. Groupe d'intérêt en Hémostase Périopératoire (GIHP) and the Groupe Français d'études sur l'Hémostase et la Thrombose (GFHT) is recommended to discontinue Tamoxifen in hospitalized patients with COVID 19 for thrombosis prevention and in patients who require thromboprophylaxis. In our opinion, the discontinuation of Tamoxifen in outpatients also will be important in preventing thrombosis.

Some researchers think that Tamoxifen can be beneficial in patients with COVID 19 [3]. In 2013, the FDA approved the use of SERMs in ebolavirus infection. Studies have been carried out considering that SERMs may show similar effects in different viruses. Studies have shown that Toremifene (another SERM) may have an antiviral effect against MERS-CoV and SARS-CoV, which are members of the coronavirus family [3]. However, the mechanism by which it gains antiviral properties is unknown. Although the question that SERMs can be used against COVID 19 comes to mind, there is no study on the subject.

Tanoxifen, stop or go?

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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