Review Article

Key points of anti-tumor treatment in breast cancer patients with SARS-CoV-2 infection

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Abstract: Internationally, the outbreak of coronavirus disease 2019 (COVID-19) has become the most serious public health emergency. With the adjustment of the prevention and control policies, China downgraded the management of COVID-19 from Class A to Class B, causing new challenges in the clinical management of patients with breast cancer. It is necessary to formulate clinical strategies for timely and reasonable anti-tumor treatment after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. By combing the relevant evidence and summarizing the anti-tumor treatment experience for breast cancer patients with SARS-CoV-2 infection in various regions, the expert panel of the Breast Cancer Professional Committee of the Chinese Society of Clinical Oncology (CSCO-BC) discussed and voted on hot and difficult issues of this situation timely. Based on the vote results, combined with domestic and foreign guidelines and consensus, the key points of treatment and management of breast cancer patients who were infected with COVID-19 have been established to provide suggestions and recommendations for clinical practice, such as restart time of anti-tumor treatment, application of anti-tumor drugs and other considerations. In the formulation of this key point, we mainly focus on mild to moderate and asymptomatic infection patients who account for the largest proportion of COVID-19 patients, and propose diagnosis and treatment recommendations for breast cancer patients with different infections and after SARS-CoV-2 infection, aiming to provide a reference for clinical diagnosis and treatment.

Keywords: Breast cancer; coronavirus disease 2019 (COVID-19); expert recommendations

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Introduction

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a profound impact on the entire society and the health care system. In fact, it changes both the lifestyles of the general public and the workflow of the medical systems. The Breast Cancer Professional Committee of the Chinese Society of Clinical Oncology (CSCO-BC) published the "Ten hot issues on diagnosis and treatment of breast cancer under the outbreak of novel coronavirus pneumonia" in *Zhonghua Yi Xue Za Zhi* in 2020 and the "Key points of breast cancer management under public health emergencies" in the *Translational Breast Cancer Research* in 2022, timely updating the committee's recommendations on breast cancer management during the COVID-19 pandemic (1,2). With the changes in virus characteristics, pandemic situation, vaccination development, medical resource preparation, and control experience, China downgraded the management of COVID-19 from Class A to Class B on January 8, 2023, and the prevention and control of this disease in China has entered a new stage. After the policy adjustment, the priority of health care will shift from infection prevention and control to medical treatment, focusing especially on high-risk populations such as the elderly people and individuals with underlying diseases. For breast cancer patients, in addition to vaccination, personal protection, and timely treatment after infection to minimize

severe disease and death from COVID-19, proper anti-tumor strategies should also be established in a timely and reasonable manner after SARS-CoV-2 infection. To facilitate the diagnosis and treatment of breast cancer in the new era, CSCO-BC reviewed the relevant evidence and summarized the anti-tumor treatment experience for breast cancer patients with SARS-CoV-2 infection in various regions. For this purpose, an expert panel was convened to discuss and vote on hot and difficult issues of clinical concern. This document reflects the experts' opinions and attitudes towards the treatment and management of breast cancer patients with SARS-CoV-2 infection, and any comments or suggestions are welcome.

China's Diagnostic and Treatment Protocol for COVID-19 (Trial Version 10) has classified COVID-19 into four clinical subtypes including mild, moderate, severe, and critical according to the signs and symptoms of the disease (3). Since the disease onset, treatments, and outcomes dramatically differ among severe and critical cases, the timing of restarting anti-tumor therapy requires multidisciplinary assessment. Focusing mainly on patients with mild, moderate, or asymptomatic infection, who account for the largest proportion of COVID-19 patients, this document attempts to offer the updated recommendations on the diagnosis and treatment of breast cancer in patients during and after SARS-CoV-2 infection.

Surgical treatment of breast cancer

Surgery is one of the main treatments for early-stage breast cancer and can dramatically improve the long-term prognosis. Recommendations for surgery priorities in breast cancer patients during the COVID-19 pandemic should be based on a comprehensive consideration of cancer biology, clinical manifestations, health status, and treatment willingness to ensure optimal disease management.

The COVIDSurg Collaborative has initiated a series of cohort studies on surgery during the COVID-19 pandemic. In a study that enrolled 20,006 patients with different cancer types, 2,003 (10.0%) did not receive surgery due to a COVID-19-related reason. Notably, unlike those for other cancers, surgery for breast cancer was not obviously affected by the restriction measures (4). Another study analyzed patients who underwent surgery for a variety of conditions between January and March 2020, and all patients had SARS-CoV-2 infection confirmed within 7 days before or 30 days after surgery. A total of 1,128 patients were enrolled, in whom the 30-day mortality reached 23.8% and the incidence of postoperative pulmonary complications was 51.2% (5). The results of a study involving 140,231 patients showed that the risk of perioperative death following SARS-CoV-2 infection decreased with the increase in time from diagnosis of SARS-CoV-2 infection to surgery. Surgery performed ≥7 weeks after SARS-CoV-2 diagnosis was associated with a similar mortality risk to baseline (6).

Although the above results suggested that surgical treatment for patients with SARS-CoV-2 infection should be performed with caution, they were less informative for current breast cancer patients: all the above data were based on the early SARS-CoV-2 strains, and few literature has described the impact of Omicron variant on surgery. Furthermore, the patients enrolled in the above studies included a variety of diseases or cancer types, and there was a lack of data specifically for breast cancer.

Therefore, the CSCO-BC expert group reached the following consensuses after consultations and voting.

Timing of COVID-19 vaccination in operable patients

Preoperative COVID-19 vaccination (preferably three doses) is encouraged (Yes: 66.67%; No: 27.16%; Others: 6.17%). In addition, the last dose of a COVID-19 vaccine should be given at least 2 weeks before surgery (Yes: 91.36%; No: 7.41%; Others: 1.23%).

For non-COVID-19 patients during the pandemic, the risks and trends of SARS-CoV-2 infection should be considered

Most surgeries can be performed as scheduled in the low-prevalence phase of the pandemic. For some patients undergoing low-risk surgeries (e.g., benign lesion resection and lactiferous ducts resection; prophylactic surgery in asymptomatic patients at high risk of morbidity; and surgery for noninvasive breast cancer), postponing the surgery may be considered on a case-by-case basis. For triple-negative and human epidermal growth factor receptor 2 (HER2)-positive patients, neoadjuvant therapies prior to surgery may be considered. In addition, patients with inflammatory and locally advanced breast cancers should receive neoadjuvant therapy prior to any surgery.

In the high-prevalence phase of the pandemic, neoadjuvant therapy is preferred for patients diagnosed with breast cancer (Yes: 60.49%; No: 27.16%; Others: 12.35%). If the tumor is small and the axillary lymph nodes are clinically negative, local tumor resection plus sentinel

lymph node biopsy can be performed, and total mastectomy and axillary lymph node dissection should be avoided (Yes: 75.31%; No: 14.81%; Others: 9.88%). For patients with a benign tumor, the mass can be observed for 1–2 months before reexaminations, and then a decision on surgery can be made (Yes: 97.53%; No: 0%; Other: 2.47%).

For patients with mild, moderate, or asymptomatic SARS-CoV-2 infection

Elective surgery should be avoided for within 7 weeks after infection unless the benefits of surgery outweigh the risks of waiting, and an individualized risk assessment should be performed for the patients (Yes: 69.14%; No: 22.22%; Others: 8.64%). Meanwhile, urgent breast cancer surgery should not be performed within 10 days after infection (Yes: 95.06%; No: 2.47%; Others: 2.47%).

Level I and II mammary procedures (e.g., hollow needle aspiration, Mammotome biopsy, and local mass resection) can be performed 1 week after a negative nucleic acid/antigen test (Yes for 1 week after a negative nucleic acid/antigen test: 66.67%; Yes for 2 weeks after a nucleic acid/antigen test: 28.4%; Yes for 1 month after a negative nucleic acid/antigen test: 4.94%). For levels III and IV surgeries, 44.4% of the experts believed that they could be performed 2 weeks after a negative nucleic acid/antigen test, whereas 43.2% believed that it should be performed 1 month after a negative nucleic acid/antigen test (Yes for 1 week after a negative nucleic acid/antigen test: 12.35%; Yes for 2 weeks after a negative nucleic acid/antigen test: 44.44%; Yes for 1 month after a negative nucleic acid/antigen test: 43.21%).

Treatment decisions for patients with other special conditions should be discussed and determined by a multidisciplinary team (MDT) and should be documented in the medical record. All decisions must be communicated with the patients, and the patients' willingness and expectations should be assessed. Meanwhile, the patients should be informed of the risks and advantages of an adjusted treatment plan in the context of the COVID-19 crisis. In addition, appropriate psychological support must be provided to patients who have their surgery delayed.

Systemic treatment of early-stage breast cancer

General principles of neoadjuvant therapy

The goals of neoadjuvant therapy are to downgrade inoperable breast cancers to operable ones, enable breast- and armpit-sparing surgeries, and obtain information about *in vivo* drug susceptibility, which in turn guides subsequent treatments to improve patient outcomes (7). The expert panel recommends that, in the high-prevalence phase of the COVID-19 pandemic, standard neoadjuvant therapy is preferred for patients diagnosed with breast cancer (Yes: 60.49%; No: 27.16%; Others: 12.35%). HER2-positive, large, or locally advanced breast cancer can be treated with trastuzumab ± pertuzumab plus albumin-bound paclitaxel (ABP) because ABP requires no pretreatment, has fewer adverse effects, and can be administered weekly or every 3 weeks (8). For hormone receptor (HR)-positive patients (especially elderly patients, patients with underlying medical conditions, or patients who cannot tolerate chemotherapy), neoadjuvant endocrine therapy (NAE) can be considered as appropriate. Aromatase inhibitors (AIs) are preferred in simple NAE. Some studies have shown that the response rate was significantly higher in the letrozole cohort than the tamoxifen cohort (9-11). The addition of ovarian function suppression (OFS) is required in premenopausal patients. Evidence also suggests that the addition of CDK4/6 inhibitors to NAE can further improve efficacy. The panel recommends that NAE may be lasted for at least three months or longer, as Dixon *et al.* found that continuing NAE for 3–6 months achieved a reduction in median tumor volume by approximately 50% and a sustained reduction by 33% for 12–24 months (12). For triple-negative breast cancer (TNBC), ABP may be applied alone or in combination with weekly carboplatin, during which the treatment response should be closely observed, and the medications should be timely adjusted according to the blood cell amounts (13).

For patients who are undergoing neoadjuvant therapy for breast cancer and infected with SARS-CoV-2, neoadjuvant therapy may cause varying degrees of immune impairment. Thus, the expert panel recommends suspending or delaying treatment (Yes for 7–10 days: 46.91%; Yes for 2–3 weeks: 46.91%; and Yes for 3–4 weeks: 6.17%). The treatment delay depends on the clinical severity classification of COVID-19 (mild, moderate, severe, and critical), the type and status of malignancy, the risk of tumor recurrence/progression due to delayed treatment, comorbidities, type and intensity of treatment, and adverse effects of the treatment regimen. If antitumor treatments are urgently required due to the rapid and uncontrollable tumor progression, they should be implemented at the discretion of the responsible oncologist (14).

Previous evidence has suggested that surgery shall be completed within 4 weeks after the completion of the neoadjuvant therapy; however, under special circumstances, it is reasonable to delay surgery for 2–4 weeks in responsive patients. For patients who have benefited from neoadjuvant therapy but can not receive surgical resection as planned, postoperative adjuvant therapy may be applied, for which other drugs may be considered first: for HR-positive breast cancer, use endocrine therapy; for HER2-positive breast cancer, stop chemotherapy and continue the previously effective targeted therapy; and for TNBC, consider oral capecitabine. In short, for patients who are temporarily unable to undergo surgery, low-toxicity, effective, and easy-to-manage drugs can be applied first, and surgery shall be timely performed when conditions permit (1).

For patients with mild, moderate, or asymptomatic SARS-CoV-2 infection

Generally, the expert panel recommends that, for patients with an asymptomatic infection, delaying the treatment for at least 10 days may be considered until symptoms improve and two negative nucleic acid/antigen tests (Yes: 85.19%; No: 9.88%; Others: 4.94%). For patients with a mild/moderate infection, delaying the treatment for at least 10 days may be considered until symptoms improve and defervescence for at least 24 hours without the use of antipyretics (Yes: 92.59%; No: 3.7%; Others: 3.7%). For the individualized patient conditions and different treatment methods, please refer to other recommendations in this article.

For patients with severe or critical SARS-CoV-2 infection

Patients with severe or critical SARS-CoV-2 infections often have poor cardiopulmonary function, which can even be accompanied by other organ failure. Therefore, it is recommended that the treatment can be delayed for at least 20 days until symptoms improve and defervescence for at least 24 hours without the use of antipyretics (Yes: 76.54%; No: 11.11%; and Others: 12.35%). Notably, the use of tamoxifen increases the risk of thromboembolism, given the high risk of thromboembolic events in critically ill patients. If severe infection develops in breast cancer patients taking tamoxifen, hormone therapy should be suspended and measures to prevent thrombosis should be used (15).

Precautions for restarting treatment

The expert panel recommends the cancer patients to receive nucleic acid testing 2 weeks after reaching the discharge criteria; restarting the treatment may be considered after the SARS-CoV-2 infection becomes negative (confirmed by 2 consecutive tests with an interval of 24 hours), and another nucleic acid test for SARS-CoV-2 is required before treatment. In view of the weak immune system in tumor patients and the possibility of re-infection, it is recommended to closely and dynamically monitor the nucleic acid testing results during subsequent antitumor treatments (16). The original treatment protocol may be applied when restarting the treatment but can also be adapted according to the patients' conditions (17). It is recommended that treatment should be adjusted to avoid potential treatment-related immunosuppression. Relevant strategies include using a three-week regimen (if possible), reducing hospital visits and admissions, avoiding intravenous administration, and avoiding other adverse effects (18). Through MDT and by communicating with patients, oncologists should carefully assess the patient's status, disease stage, and treatment goals and preferably use oral drugs and long-cycle regimens under the premise of the same efficacy.

General principles of postoperative adjuvant therapy

For patients with early-stage breast cancer, the goals of postoperative adjuvant therapy are to prolong disease-free survival (DFS) and reduce the probability of tumor recurrence, especially for high-risk patients. During the COVID-19 pandemic, the choice of adjuvant treatment regimen for patients with early-stage breast cancer and the decision on delaying the treatment should be based on a comprehensive consideration of the clinical classification of SARS-CoV-2 infection, clinicopathological stage of tumors, and other factors. In the high-prevalence phase of the pandemic, for patients who are undergoing neoadjuvant/adjuvant therapy for breast cancer and infected with SARS-CoV-2, neoadjuvant/adjuvant therapy may cause varying degrees of immune impairment. Thus, the expert panel recommends suspending the treatment for 1–3 weeks based on health status of the patient (Yes for 7–10 days: 46.91%; Yes for 2–3 weeks: 46.91%; and Yes for 3–4 weeks: 6.17%). If antitumor treatments are urgently required due to the rapid and uncontrollable tumor progression, they should be implemented at the discretion of the responsible oncologist (14).

Chemotherapy

During the COVID-19 pandemic, indications for

postoperative adjuvant chemotherapy must be strictly followed to avoid unnecessarily high dose intensity. For non-infected patients who may require adjuvant chemotherapy, the expert panel recommends: For HR-positive breast cancer patients with 1–3 positive axillary lymph nodes, multigene testing shall be performed, and the need for chemotherapy should be determined after assessing the recurrence risk. For patients who need chemotherapy, carefully weigh its pros and cons and try to choose a chemotherapy regimen with low risk of granulocytopenia. Strictly calculate the chemotherapy dose and never exceed the maximum recommended dose. Prophylactic leukocyte-raising measures should be strictly implemented during chemotherapy, for which long-acting granulocyte colony-stimulating factor (G-CSF) for primary prophylaxis is recommended. Postoperative chemotherapy can be delayed for 2 to 8 weeks, up to 12 weeks (17,19). The treatment-free interval between cycles should be as long as possible (e.g., 2-week or 3-week schema) (15).

During the adjuvant chemotherapy, the treatment shall be reasonably adjusted in light of the patient's condition, so as to minimize the impact of the pandemic on treatment and minimize the risk of getting more serious symptoms due to decreased immunity after chemotherapy. For infected patients undergoing intravenous chemotherapy, chemotherapy can be resumed 1 or 2 weeks after negative nucleic acid/antigen tests (Yes for immediate re-starting: 4.94%; Yes for after 1 week: 55.56%; and Yes for after 2 weeks: 39.51%). For some HR-positive breast cancer patients who are receiving chemotherapy, if adjuvant chemotherapy is interrupted due to epidemic control policies and will not resume within a short period of time, endocrine therapy may be performed first.

Targeted therapy

For patients who are undergoing adjuvant targeted therapy, a delay of 6–8 weeks has little impact on overall efficacy resume in the high-prevalence phase of the pandemic. After the therapy is resumed, a loading dose can be re-administered; or, the intervals among subsequent doses can be adjusted appropriately to ensure a 12-month treatment course. For infected patients who are receiving anti-HER2 therapy, the expert panel generally believe that the treatment should be suspended for 2 weeks until negative nucleic acid/antigen tests (Yes: 88.9%; No: 6.17%; Others: 4.94%). The duration of adjuvant therapy with trastuzumab can be shortened to 6 months in some HER2-positive, low-risk [clinical stage I–II or achieving pathological complete response (pCR) after neoadjuvant treatment], elderly breast cancer patients with cardiovascular diseases (20). In patients who do not achieve pCR after neoadjuvant chemotherapy, trastuzumab emtansine (T-DM1) or tyrosine kinase inhibitor (TKI) may be considered as an alternative adjuvant treatment (12). If intravenous therapy is not available for an extended period of time, a temporary switch to an oral TKI may be considered.

Endocrine therapy

For patients with HR-positive breast cancer, adjuvant endocrine therapy can be used after chemotherapy or directly applied in low-risk patients who do not need chemotherapy. Oral AIs or selective estrogen receptor modulators (SERMs) are the treatment of choice. For high-risk patients, CDK4/6 inhibitors may be added (21); however, patient education and proactive adverse event (e.g., neutrophils and diarrhea) management are critical. Endocrine therapy may be appropriately delayed in high- and medium-risk premenopausal patients who need OFS if OFS drugs can not be injected after SARS-CoV-2 infection. SERM monotherapy can be used first. For infected patients undergoing endocrine therapy alone, the expert panel generally believes that the original treatment schema can be continued after negative tests. However, for patients also treated with CDK4/6 inhibitors, it is recommended to re-evaluate clinical indicators such as blood cell amounts and liver and kidney function, and these drugs may be re-used after gastrointestinal symptoms are alleviated. If the SARS-CoV-2 infection occurs during SERM use, it is recommended that SERMs should be suspended and antithrombotic drugs can be used prophylactically considering that COVID-19 may cause thromboembolism and SERMs may increase the risk of thrombosis. Adjuvant endocrine therapy should be given for 5 to 10 years to ensure the intensity and continuity of treatment.

Immunotherapy

The immune-related adverse events (irAEs) of immunotherapy are somehow similar to the clinical manifestations of COVID-19 (22). For patients with SARS-CoV-2 infection, immunotherapy may aggregate the symptoms of COVID-19. For infected patients who are receiving anti-HER2 therapy, the expert panel recommends that the immunotherapy should be suspended for 2 weeks until negative nucleic acid/antigen tests (Yes: 95.06%; No: 3.7%; Others: 1.23%). The immunotherapy can be re-started six weeks after radiotherapy and chemotherapy, and

the interval between immunotherapy can be appropriately extended [pembrolizumab: extended from every 3 weeks (Q3W) to every 6 weeks (Q6W)]. Regular chest CT is recommended to observe tumor changes during the extension period (23).

Systemic treatment of advanced breast cancer

The goals of treatments for advanced breast cancer are to prolong survival and improve the quality of life. Because patients with advanced breast cancer are always tumor-bearing, the risks and benefits of systemic treatment should be weighed when making clinical decisions during SARS-CoV-2 infection. During the COVID-19 pandemic, the timing and intensity of anti-tumor therapy should be based on the molecular type of breast cancer, tumor burden, tumor progression, and physical status of the patients.

There is no clear evidence on the optimal timing and modality of anti-tumor therapy for patients with advanced breast cancer during or after SARS-CoV-2 infection. Based on the voting results, the Chinese and foreign consensuses/guidelines (14,16,24), and drug treatment patterns and adverse reaction spectra, the following recommendations are made.

Patients with HR-positive HER2-negative advanced breast cancer

In most patients with $HR^+/HER2^-$ advanced breast cancer without visceral crisis, endocrine therapy alone or in combination with other drugs is the mainstay of treatment.

The basic principle of endocrine therapy alone is to lower the levels of estrogen or estrogen receptors, and the treatment drugs have less impact on the blood system, metabolic system, or immune system. Therefore, the expert panel recommends that: for patients with advanced breast cancer who have not had abnormal hematology or liver/kidney function during previous endocrine therapy, endocrine therapy may not be suspended during mild or moderate COVID-19 (Yes: 85.19%; No: 14.81%; Others: 0%); however, patients with severe COVID-19 should avoid taking SERMs such as tamoxifen to avoid thromboembolic events (11,15); for patients who have previously experienced abnormal blood system or liver and kidney function due to the use of endocrine therapy drugs, it is recommended to suspend endocrine therapy for 2 weeks during COVID-19 until negative nucleic acid/antigen tests (Yes: 85.19%; No: 13.58%; Others: 1.23%) to avoid cross-reactions between endocrine therapeutics and drugs used to treat fever (such as acetaminophen and ibuprofen) or other drugs metabolized by the liver or kidney. The common adverse effects of CDK4/6 inhibitors, chidamide, and everolimus are the decrease in neutrophils, leukocytes, and lymphocytes, and everolimus can also suppress the immune system (17). The expert panel generally believes that targeted therapy should be suspended for 2 weeks during SARS-CoV-2 infection until negative nucleic acid/antigen tests. For patients who have not experienced any grade of neutropenia during a prior CDK4/6 inhibitor treatment, the treatment may be continued under close monitoring of blood cell count (Yes: 56.79%; No: 39.51%; Others: 3.7%) after a thorough assessment of the potential risk of fever.

For patients with $HR^+/HER2^-$ advanced breast cancer with visceral crisis or rapid progression, prior evidence often suggests salvage chemotherapy. New evidence also indicates that CDK4/6 inhibitors combined with endocrine therapy can be used as a new clinical option (25). Therefore, the expert panel recommends that the treatment decision should be individualized after a comprehensive assessment of the tumor burden, symptoms of COVID-19, and patient's performance status and by weighing the risks and benefits of the treatments.

Patients with HER2-positive advanced breast cancer

The currently available anti-HER2 drugs include monoclonal antibodies, antibody-drug conjugates (ADCs), and small molecule TKIs. Monoclonal antibodies inhibit tumors via antibody-dependent cell-mediated cytotoxicity (ADCC), which will activate immune effector cells such as natural killer (NK) cells, macrophages, and neutrophils and thus aggravate the damage of human immune system during SARS-CoV-2 infection (26). The expert panel recommends that monoclonal antibodies should be suspended for 2 weeks until negative nucleic acid/antigen tests (Yes: 88.89%; No: 6.17%; Others: 4.94%). Anti-HER2 ADCs also have ADCC, and their common adverse reactions include headache, diarrhea, musculoskeletal pain, fever, and interstitial pneumonia, an adverse effect of concern, which overlap with some symptoms of COVID-19 (27). The expert panel recommends that ADCs should be suspended for 2 weeks until negative nucleic acid/antigen tests (Yes: 88.89%; No: 6.17%; Others: 4.94%). The common adverse reactions of small molecule anti-HER2 TKIs include diarrhea, nausea, vomiting, and rash, which overlap with some symptoms of COVID-19. The expert panel recommends that TKIs should be suspended for

2 weeks until negative nucleic acid/antigen tests (Yes: 83.95%; No: 11.11%; Others: 4.94%).

For patients with high tumor burden and critical tumor conditions, the expert panel recommends that the treatment decision should be individualized after a comprehensive assessment of the tumor burden, symptoms of COVID-19, and patient's performance status and by weighing the risks and benefits of the treatments.

Patients with triple-negative advanced breast cancer

Chemotherapy is the main treatment for advanced TNBC. A common adverse reaction during chemotherapy is a decrease in white blood cells (including neutrophils, NK cells, and lymphocytes), resulting in impaired immune function and aggravating symptoms of COVID-19 infection (28). Even though there are some data suggesting that chemotherapy has no significant effect on mortality related to COVID-19 infection (29), considering the superposition of adverse reactions caused by chemotherapy and symptoms related to COVID-19 infection, if the patient's tumor disease is under stable control, the expert panel recommends that, for infected patients who are undergoing salvage intravenous chemotherapy for the advanced breast cancer, the intravenous chemotherapy may be suspended until 1 or 2 weeks after negative nucleic acid/antigen tests (Yes for more than 1 week: 49.38%; Yes for more than 2 weeks: 43.21%; Yes for immediate: 7.41%) according to individual circumstances. Even in patients receiving oral chemotherapy drugs such as capecitabine/vinorelbine, suspending the use of these drugs should also be considered with close monitoring of blood cell profiles (Yes: 64.2%; No: 34.57%; Others: 1.23%). When restarting chemotherapy, a decision to lower the dose or switch treatment regimen can be made based on whether patients have COVID-19-related sequelae (30).

The main immunotherapy drugs for advanced TNBC are anti-programmed cell death protein 1/programmed death ligand 1 (anti-PD-1/PD-L1) monoclonal antibodies. Previous studies have revealed that tumor patients treated with anti-PD-1/PD-L1 monoclonal antibodies had a higher incidence of severe events and mortality after SARS-CoV-2 infection (31,32). There is also evidence suggests that anti-PD-1/PD-L1 monoclonal antibodies have a potential therapeutic effect on COVID-19, although such a clinical value remains to be verified (33). At present, there is limited clinical evidence on the role of anti-PD-1/PD-L1 monoclonal antibody therapy in breast cancer patients with COVID-19. The currently available international guidelines recommend that immunotherapy should be suspended after SARS-CoV-2 infection and restarted after the patients recover (14,34). Therefore, the expert panel recommends that, for infected patients who are receiving immunotherapy, the immunotherapy should be suspended for 2 weeks until negative nucleic acid/antigen tests (Yes: 95.06%; No: 3.7%; Others: 1.23%).

Other issues

Follow-up visits

According to the European Society for Medical Oncology (ESMO) guidelines on the management and treatment of breast cancer during the COVID-19 pandemic, for patients with early-stage or advanced breast cancer (including those at high risk of recurrence), a 6–8-week delay in visits during the COVID-19 pandemic is acceptable if the tumor is stable. Symptom-oriented follow-up visits, including delays in imaging, clinical staging, echocardiography, electrocardiogram, and bone scan, are recommended (15).

The expert panel suggests that routine re-examinations for breast cancer can be postponed after SARS-CoV-2 infection according to the individual conditions of the patients, and these re-examinations can be normally performed after negative nucleic acid/antigen tests (Yes for normal re-examinations immediately after negative nucleic acid/antigen tests: 60.49%; Yes for postponed by 1 month: 28.4%; Yes for postponed by 2 months: 11.11%).

Bone-modifying agents in the treatment of bone metastasis

In the OPTIMIZE-2 study, breast cancer bone metastasis patients who had previously received a standard regimen of zoledronic acid and/or pamidronate were randomized to receive zoledronic acid every 4 or every 12 weeks; it was found that the every 12 weeks regimen of zoledronic acid was noninferior to the every 4 weeks regimen for the proportion of patients experiencing 1 or more skeletal-related events (SREs) (35). Therefore, both the Cancer and Bone Society (CABS) guidelines and ESMO guidelines on the management of breast cancer bone metastasis during the COVID-19 pandemic proposed that, for the infected patients with breast cancer bone metastasis who are being treated with a bone-modifying agent (zoledronic acid or denosumab), either adjuvant treatment or salvage treatment can be performed every three months (15,36,37).

The common adverse events of bisphosphonates (zoledronic acid, ibandronic acid, etc.) and denosumab include acute phase reactions (i.e., transient fever, bone pain, and myalgia shortly after infusion), especially in patients treated with zoledronic acid (38). These symptoms may exacerbate COVID-19. The expert panel recommends that, for infected patients who are being treated with a bone-modifying agent, the treatment should be postponed until tested negative for SARS-CoV-2 (Yes for immediately after turning negative: 45.68%; Yes for more than 1 week after turning negative: 28.4%; Yes for more than 2 weeks after turning negative: 25.93%).

Myocardial enzyme test prior to restarting therapy with specific drugs

SARS-CoV-2 infection can cause damage to multiple organs, among which the cardiac complications such as myocarditis are of particular concern. According to the "2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults", about 40% of hospitalized COVID-19 patients had myocardial injuries of varying degrees (39). Acute myocardial injury occurs in severe COVID-19 cases, manifested as elevated high-sensitivity troponin (hs-TnT) in ancillary tests (40-42).

Anthracyclines are widely used in the treatment of breast cancer, but they can directly damage cardiomyocytes by triggering oxygen free radical generation and promoting myocardial oxidative stress, resulting in lipid peroxidation of the cardiomyocyte membrane and damage to myocardial mitochondrial DNA (mtDNA) and thereby directly injuring the cardiomyocytes. The cardiotoxicity is irreversible (43). In addition, anti-HER2 drugs (e.g., trastuzumab) may damage cardiomyocytes and cause cardiotoxicity through a variety of pathways such as HER2 blockade and increased production of reactive oxygen species (44).

Therefore, for infected patients with breast cancer, if the restarted therapies contain anthracyclines or anti-HER2 monoclonal antibodies, routine cardiac enzyme testing is required in addition to routine periodic cardiac ultrasound and electrocardiogram, so as to avoid aggravating myocardial damage (Yes: 92.59%; No: 7.41%; Others: 0%).

Primary prophylactic use of G-CSF

In a retrospective study, the use of G-CSF in tumor patients with both COVID-19 and neutropenia might lead to deterioration of clinical and respiratory statuses (45). Another open-label, multicenter, randomized clinical trial conducted in China, recombinant human granulocyte colony-stimulating factor (rhG-CSF) treatment for patients with COVID-19 with lymphopenia but no comorbidities did not accelerate clinical improvement, but the number of patients developing critical illness or dying might have been reduced (46). To reduce the risk of febrile neutropenia, both American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines recommend that consideration should be given to expanding the standard for prophylactic treatment with G-CSFs in tumor patients and appropriately strengthening primary prophylaxis (47,48). Therefore, for patients who continue breast cancer treatment after SARS-CoV-2 infection, the expert panel recommends the use of long-acting G-CSF for the primary prophylaxis of bone marrow suppression (if there is such a risk) (Yes: 92.59%; No: 3.70%; Others: 3.70%).

Radiotherapy

In principle, the adjuvant radiotherapy shall be completed within 6 months after surgery. However, a delay of 1 to 2 months may be considered during the COVID-19 control period because the patients cannot go to the hospital for radiotherapy, avoid frequent visits to hospitals and communities, or worry about radiation-induced pneumonitis and decreased immunity after radiotherapy (49). Adjuvant endocrine therapy or targeted therapy may be applied first. Once conditions permit, adjuvant radiotherapy should be prioritized for patients with high-risk breast cancer (e.g., young patients, inflammatory breast cancer, large or axillary lymph node-positive patients, TNBC or HER2-positive breast cancer, and positive margins after a breast-conserving surgery). For advanced breast cancer, the ESMO guidelines recommend prioritizing radiotherapy in patients with acute spinal cord compression, symptomatic brain metastases, and other factors that may affect survivals or quality of life (15). For the timing of radiotherapy suspension, the expert panel recommends that: for the infected patients who are receiving radiotherapy, computed tomography (CT) should be performed before re-radiotherapy to assess whether there is pneumonia (Yes for suspending radiotherapy for more than one week: 20.99%; Yes for suspending radiotherapy for more than two weeks: 8.64%; and Yes for assessing for pneumonia with CT before re-radiotherapy: 70.37%). The priority patient population also include patients who

had received radiotherapy but whose radiotherapy course was interrupted due to the implementation of COVID-19 pandemic. For elderly patients with low-risk breast cancer who are undergoing adjuvant endocrine therapy, the expert panel recommends to assess the benefit-risk ratio first before deciding whether the postoperative radiotherapy can be waived (15).

Prophylactic use of anticoagulants

Coagulation abnormalities were found in nearly 20% of COVID-19 patients, and some studies have shown that anticoagulation therapy in COVID-19 patients could effectively reduce the mortality (50,51). According to the US National Institutes of Health (NIH) guidelines, routine prophylactic use of anticoagulants is not recommended in non-hospitalized patients without evidence of venous thromboembolism (52). China's Diagnostic and Treatment Protocol for COVID-19 (Trial Version 10) recommends anticoagulation for moderate cases with risk factors for severe disease and rapid progression as well as for severe and critical cases (3). Therefore, the expert panel recommends that the benefits and risks of anticoagulation should be fully assessed in infected patients with breast cancer because some drugs for breast cancer may cause venous thromboembolism; however, routine prophylactic anticoagulation is not required (Yes: 69.14%; No: 27.16%; Others: 3.7%). In the event of thromboembolic events, symptomatic treatment can be performed according to the corresponding guidelines.

The impact of the COVID-19 pandemic on breast cancer management is extremely complex, and there is currently a lack of high-quality research data. We must recognize the risk of SARS-CoV-2 infection, understand its pathogenic characteristics and impact on breast cancer treatment, and make reasonable clinical decisions to minimize the impact of the pandemic on the management of breast cancer patients. The Breast Cancer Expert Committee of the Chinese Society of Clinical Oncology will work together with all the breast cancer oncologists across China to review the latest data on the management of SARS-CoV-2-infected breast cancer patients in China and release treatment opinions in a timely and efficient manner, so as to inform clinicians. It can be expected that the management measures will be adjusted with the emerging of new SARS-CoV-2 variants and the advances in breast cancer treatment, and more evidence is warranted to support our clinical decisions.

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Footnote

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Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://tbcr.amegroups.org/article/view/10.21037/tbcr-23-10/coif). The author has no conflicts of interest to declare.

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