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Review Article

Breast Cancer Management during the COVID-19 Pandemic: A Review of the Dynamic and Evolving Guidelines and Some Personal Thoughts

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Abstract

Nearly, every country around the world is being challenged in every direction by the lethal infectious disease known as COVID-19. The COVID-19 viral pandemic accountable for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease has drastically influenced our work worldwide in the management of patients in terms of diagnosis and surgical treatment of cancer - including breast cancer. In fact, oncology practice has been transformed in response to this crisis. Today, more than ever, oncologists are postponing chemotherapies, delaying curative surgeries and switching intravenous to oral therapies. This is due to the fact that cancer patients are at a significantly higher risk of getting infected with COVID-19 since their immune system can be compromised. The reality has to do with both that they have cancer and that they are on therapy for their cancer. As medical oncologists, it is our duty to make sure that these cancer patients are treated appropriately with a minimal exposure risk to this crushing virus. Herein, we are presenting a review that introduces the evolving guidelines for management of breast cancer patients in view of this pandemic, along with various methods of risk classifications. We also sought to include a personal analysis and hypothesis for the best optimal oral treatment in a particular bundle of breast cancer patients.

Keywords: SARS-CoV-2; COVID-19; Breast Cancer

Introduction

A pandemic-by definition- is a disease outbreak which extends across countries and continents. On March 11, 2020, the World Health Organization acknowledged a new pandemic- COVID-19 caused by a novel coronavirus, SARS-CoV-2. Taken by surprise after its rapid spread around the world, the medical community suffered

first and foremost. COVID-19 crisis impacted every aspect of the practice from outpatient clinics to internal wards and surgery procedures [1].

Patients with chronic illnesses were the most vulnerable of all population. Same as any infectious disease, people with compromised health are at increased risk for COVID-19 infection, including the nineteen million individuals with cancer and other survivors [2].

People affected by cancer are more prone to infections owing to their immunosuppressive state caused by both the cancer itself and its treatment. Thus, cancer patients who contact the SARS-CoV-2 virus are expected to develop a more severe disease course with higher admission rate to intensive care unit. However, data concerning COVID-19 and cancer remains scant [3].

Breast cancer during the pandemic

In the efforts to restrict the flow of COVID-19 cases to the Emergency departments, general hospitals and cancer centers imposed long-term strategies to protect the vulnerable population. Changes included but were not restricted to delaying non-urgent surgeries, minimizing follow-up visits thus expanding home-based therapies, and encouraging the use of telehealth. For breast cancer patients in particular, the genomic tumor profiling approach increased during the pandemic to guide neo-adjuvant therapy decision thus decreasing surgery referrals. As such, a multidisciplinary attitude for breast cancer treatment is required [4].

A retrospective double-cohort study done across the Kaiser Permanente Northern California (KPNC) health care system, assessed the presentation and treatment patterns of patients diagnosed with breast cancer between March 17th and May 18th, 2020 (n = 703) to patients diagnosed between the same period in 2019 (n = 250). Compared to patients diagnosed in 2019, those diagnosed during the COVID- 19 pandemic presented with a more advanced stage and aggressive disease of breast cancer. For instance, a non-statistically significant trend towards increase in metastatic disease from 2% to 7% was reported in 2020. Triple negative breast cancer rate increased from 10% in 2019 to 16% in 2020 ($p = 0.04$) [5]. As for treatment, 15% of patients diagnosed in 2020 underwent neoadjuvant chemotherapy compared to 10% in 2019. Whereby surgery was the preferred standard of care in 2019 (83% v/s 71%; $p < 0.001$). These results highlight the importance of screening for the early detection of breast cancer and prompt intervention [5].

General and disease specific (breast cancer) guidelines for cancer care

As COVID-19 vaccine has become a reality over the past few months, we cannot simply disregard the primary and most important safety measures - mask and social distancing. During the process of vaccinating the world population, with prioritizing healthcare workers and elderly first, standards for treatment care and goals for patients with breast cancer and other chronic diseases (malignant or benign conditions) became a pressing matter. The aim for patient treatment includes long-term clinical outcomes, reduce patient interactions with healthcare centers, preserve patient safety and, protect patients from treatment side-effects namely immunosuppression. Therefore, breast cancer societies around the world compiled recommendations aimed for patient care and safety [1].

Classifications

Patient classifications

The consortium of organizations categorized patients with breast cancer into three priorities: A, B, and C. Priority A includes patients with oncologic emergencies such as febrile neutropenia, hypercalcemia, and intolerable pain who need immediate treatment because of rapid deterioration and life-threatening situation.

Priority B patients do not require urgent treatment; however, treatment cannot be indefinitely delayed. Patient profiles were further directed to sub-division by severity of the disease. For instance, B1 sub-group recommendations are to consider neoadjuvant therapy for patient with inflammatory breast cancer (BC), refer to surgery or change therapy for patient progressing on neoadjuvant treatment, and complete therapy for patients who already started chemotherapy or neo-adjuvant systemic treatment. Patients with estrogen receptor (ER) positive ductal carcinoma in situ are categorized as B3, and recommendation is to start neoadjuvant endocrine therapy to defer surgery. Also in this subgroup are patients with human epidermal growth factor receptor (HER2) positive BC on adjuvant anti-HER2 treatment whereby it is proposed to shorten treatment to 6 to 9 months instead of 12 months.

Finally, priority C patients are those whose treatment or follow-up can be postponed during the pandemic with no repercussions on the patients' health [6].

Treatment classifications

The European Society for Medical Oncology (ESMO) suggested dividing breast cancer patients receiving treatment into three groups. The high-priority group are unstable patients with a large cancer burden requiring immediate treatment. As for the medium-priority group, these are patients whose treatment can be delayed more than six weeks with no concerns of harmful side-effects with this delay. Finally, patients where care can be deferred till the end of the pandemic are classified as low-priority [1].

Health care system and hospital evaluation

The American College of Surgeons (ACS) evaluated the health system and hospitals in three phases according to the community's resources and health workers. Phase 1 is considered when the number of COVID-19 patients admitted is low with sufficient resources. In this phase, it is appropriate to consider surgery instead of neo-adjuvant chemotherapy. More notably, urgent procedures such as drainage of a breast abscess, hematoma evacuation, revision of an ischemic mastectomy flap or autologous tissue flap should be treated as promptly as possible. Phase 2 is considered when the number of COVID-19 patients has increased and if hospitals have limited resources. Phase 3, is when hospital resources are insufficient with fully occupied beds with COVID-19 patients. In the latter two phases, neo-adjuvant chemotherapy should be considered for selected patients [1].

Breast imaging classification

Breast imaging recommendations and prioritization were also proposed given the rapidly evolving COVID-19 pandemic and the necessity to protect breast cancer patients. For Priority A, situations include imaging for breast abscess or imaging for evaluation of a post-operative complication. Patients undergoing imaging in Priority B are those with an abnormal mammogram and require diagnostic investigations, patients who need evaluation of extent of disease by breast MRI, or those with BI-RADS 4 or 5 lesions and require biopsies. Breast imaging Priority C comprise imaging that can be delayed until after the COVID-19 period; these include screening imaging and ultrasound or mammogram for BI-RADS 3 category patients [6].

Special population management

High-risk lesions and pre-invasive breast cancer

During the pandemic, according to the American Cancer Society (ACS), surgical management of DCIS should be deferred. For instance, intervention for ER negative DCIS should be deferred for a minimum of 3 to 6 months and even delayed after the pandemic peak when surgical supplies are more available [4].

While ER positive DCIS are managed in the meantime through a telemedicine consultation with the oncologist, patients shall be placed on neoadjuvant endocrine therapy for a period of up to 6 months. Aromatase inhibitor is the proper choice for postmenopausal women while tamoxifen for premenopausal women [4].

For the proportion of patients with ER positive DCIS that had been previously managed with a breast conserving surgery, we recommend delaying radiation and managing instead with endocrine therapy. In fact, patient with good risk disease, i.e. low to intermediate grade, less than 2.5 cm, surgical margins more than or equal to 3mm, radiation therapy can be omitted [4].

Invasive breast cancer - advanced stage

Many treatment options exist for patients with metastatic advanced BC. This population receives several treatment lines that are rarely based on precise sequencing of therapy. To minimize clinic visits, laboratory workup as well as the development of serious side effects, systemic medication dosage and schedule changes are appropriate. In addition, if the patient does not show signs or symptoms indicative of progression of disease, restaging scans can be delayed as well. In cases when the potential gain of additional palliative chemotherapy is very limited, patients may find that the risk of undergoing treatment overrides the benefit [6].

HER2-targeted therapeutic drugs such as trastuzumab and pertuzumab given as adjuvant treatment for HER2 positive breast cancers, may be administered at less frequent interval. In particular, patients with HER2 positive BC that have been on maintenance trastuzumab- based therapy with tumor control for longer than 2 years and minimal disease burden can interrupt their therapy [7].

In comparison, ER positive metastatic breast cancer patients offered oral targeted agents including cyclin dependent kinase 4 and 6 (CDK4/6), mechanistic target of rapamycin (mTOR), and phosphatidylinositol 3-kinase (PIK3CA) inhibitors are at increased risk of adverse events. The choice of the following therapy must be weighed against the risk of side effects. Effectively, dose reductions can be of added value thus minimizing the risk of the adverse events. For instance, lower dose of palbociclib, a CDK4/6 inhibitor

than the usual dose is efficacious, as it per the PALOMA-3 phase III trial [8].

Endocrine treatments during the pandemic

Interestingly, the category of endocrine therapy such as tamoxifen, aromatase inhibitors, luteinizing hormone releasing hormone (LHRH) agonist are considered safe and can be continued throughout this pandemic. [6] Three-monthly injections of LHRH agonists may be given instead of monthly intervals; add to that, home administration is also an option [9].

Supportive care and additional considerations

Additional considerations include supportive care for patients on chemotherapy for the aim of reducing side effects as much as possible. For example, patients should be offered granulocyte colony stimulating factor (G-CSF) to minimize risk of neutropenia even for patients on regimens that carry a risk of less than 20% of neutropenic fever. This population usually is not offered G-CSF however this is not the case in the pandemic [6].

Interventions to relieve symptomatic patients can continue to be a high priority.

While patients without hypercalcemia, bone modifying therapy like intravenous bisphosphonates or denosumab can be delayed [6].

Conclusion

It is important to note that whenever there is suspicion of oncological emergencies, severe symptoms, new diagnosis, progression and recurrence, in-person clinic visits is recommended and appropriate despite the risk of exposure to the virus for both parties; patients and providers. This does not apply for routine follow up echocardiograms and ECGs in absence of known cardiac problems. Either deferring or at least extending the intervals of monitoring is recommended [4]. As suggested previously, the aim is to adjust the therapy for two main purposes: decrease risk of immunosuppression and medical visits whenever applicable. This can be achieved by oral regimens or less frequent dosing for intravenous therapy. In addition, prophylactic G-CSF has an important role. To reduce risk of immunosuppression, we should also minimize the use of steroids when possible [4]. Briefly, align the risks of delaying or pursuing less aggressive cancer care with the risks of exposure to and infection with COVID-19 virus. Maintaining balance is the key.

Personal thoughts and considerations while treating HR (+) HER2 (-) MBC

Firstly, diarrhea as a side effect of the given therapy can mimic symptoms of COVID-19 infection leading to more visits to clinic or emergency room and thus increases likelihood of exposure [10]. Among then CDK 4/6 inhibitors, Abemaciclib was associated with diarrhea compared with Palbociclib and Ribocilcib: 86% of the patients enrolled in MONARCH-3 trial, and 82% of the patients in MONARCH-2 trial had diarrhea of any grade [11,12] (Table 1). Moreover, diarrhea occurred in 30% (all grades) in BOLERO-2 trial with Everolimus, and 2 % were grade III [13].

Secondly, neutropenia is a major risk factor during COVID-19 infection. It can also be a consequence of the viral infection. The most

Pivotal Trials	PALOMA-2	MONALEESA- 2	MONARCH-3	MONALEESA-7	PALOMA-3	MONARCH-2	MONALEESA-3
Diarrhea (Grade III/lV)	1.4/1	1.2/0	9.5/1.2	1/0	1.4/0	13.4/0	0.6/0.8
Neutropenia (Grade III/IV)	66.4/1.4	50/9.6	21.1/1.2	61/4	56/10	23/3	46.6/0
Febrile neutropenia	1.8/0	1.5/0	0/0	NR	1.8/0	1.3/0	1/0
QTc prolongation (Grade III/IV)	NR	11	NR	1	NR	NR	6.2

Table 1: Incidence of grade III/IV diarrhea, neutropenia (and febrile neutropenia), QTc prolongation with Palbociclib, Ribociclib and Abemaciclib as per the phase III randomized clinical trials/programs PALOMA, MONALEESA and MONARCH respectively [10-12,14,15,17-19].

adverse events encountered with CDK 4/6 inhibitors is neutropenia where Palbociclib and Ribociclib are associated with a higher risk of neutropenia compared with Abemaciclib due to the different affinity and inhibition of CDK 4 and CDK 6. Nevertheless, the risk of febrile neutropenia is very low (Table 1) [10-12,14,15,17-19].

Add to that, not only drugs prescribed for COVID-19 such as quinolones, azithromycin and hydroxychloroquine but also the endocrine therapy in patients with MBC increase risk of QTc prolongation, leading also again to frequent monitoring and hospital visits with the eventual increased risk of exposure. Among the three CDK 4/6 inhibitors, Ribociclib was associated with increase risk of QTc: grade III/IV QTc prolongation was reported in 11 % of the patients in MONALEESA-2 and 6.2 % of the patients in MONALEESA-3 (Table 1) [10-12, 14,15,17-19].

Venous thromboembolism (VTE) is highly prevalent in COVID 19 infections. Similarly, Tamoxifen and Fulvestrant have been previously linked with an increased risk of VTE including DVT and PE [11]. Hence, patients receiving this specific endocrine therapy and gets infected with the virus, the overall risk of VTE is exacerbated [10]. On the other side, 5% of patients treated with abemaciclib + non-steroidal aromatase inhibitor in MONARCH-3 and 2% of patients treated with abemaciclib + fulvestrant in MONARCH-2 developed VTE [11,12]. Controversially, VTE wasn't a concern with Palbociclib nor with Ribociclib, as per PALOMA and MONALEESA programs respectively [14,15,17-19].

Another important consideration is the risk of pneumonitis with Everolimus in specific and pneumonia being also a life-threatening complication of COVID-19 infection [13].

Is Palbociclib (IBRANCE ©) the safest during COVID-19 pandemic: From pivotal randomized clinical trials to real world evidence

Randomized control trials for Ibrance lead to real world evidence and reinforced the importance of this drug in patients with HR+/HER2-ABC. Not only it led to substantial prolonged progression-free survival, but also patients maintained a good quality of life similar to that of a normal healthy population. Palbociclib proved a powerful clinical efficacy regardless of the baseline characteristics: different patient age (pre/peri or postmenopausal), patients with visceral/bone metastasis, different tumor grade or progesterone receptor status, and divergent histological subtype (ductal or lobular). Among other advantages, was the fact that one pill administered once daily lead to an excellent adherence rate. Ibrance established a safety profile, however neutropenia was an adverse event, but easily managed. Thus, patient should only be monitored with CBC. Furthermore, this therapy delayed the initiation of subsequent chemotherapy. At last, in the post hoc analysis of PALOMA-2, the combination of palbociclib and letrozole showed prolonged progression-free survival and a consistent safety profile in ER+ HER2 - ABC patients regardless of their preexisting medical conditions (gastro-intestinal, vascular, cardiac, musculoskeletal, metabolic syndrome) [10,14-16].

Conflict of Interest

All authors declare no conflicts of interest.

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