Weathering the Storm: Managing Older Adults With Breast Cancer Amid COVID-19 and Beyond

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Abstract

Caring for older patients with breast cancer presents unique clinical considerations because of preexisting and competing comorbidity, the potential for treatment-related toxicity, and the consequent impact on functional status. In the context of the COVID-19 pandemic, treatment decision making for older patients is especially challenging and encourages us to refocus our treatment priorities. While we work to avoid treatment delays and maintain therapeutic benefit, we also need to minimize the risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposures, myelosuppression, general chemotherapy toxicity, and functional decline. Herein, we propose multidisciplinary care considerations for the aging patient with breast cancer, with the goal to promote a team-based, multidisciplinary treatment approach during the COVID-19 pandemic and beyond. These considerations remain relevant as we navigate the "new normal" for the approximately 30% of breast cancer patients aged 70 years and older who are diagnosed in the United States annually and for the thousands of older patients living with recurrent and/or metastatic disease.

Even during "normal" times, taking care of aging patients with breast cancer, particularly those with competing comorbidities, is challenging. In the era of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), clinicians and patients now face an extra layer of considerations. These unprecedented issues touch all patients but are particularly daunting for older patients with cancer who simultaneously face excessive risks of death from COVID-19 (1–4). More than ever before, we must critically explore patients' priorities while determining the optimal sequence, intensity, frequency, and duration of their treatments. Older women carry a preexisting risk for worse breast cancer outcomes than their younger counterparts and are at heightened risk for both undertreatment and overtreatment in the context of the COVID-19 pandemic (5).

Each treatment we consider (other than perhaps hormonal therapy) will result in some additional risk and potential exposures for a patient (and the staff who interact with that patient) while limiting our patients' ability to implement the social distancing that protects them. Even a straightforward breast surgery necessitates patient exposures to preoperative, intraoperative, and postoperative hospital staff and equipment as well as unquantifiable risks of anesthesia and periprocedure ventilation. Breast surgeries, like all other surgeries, also limit operating room availability, use personal protective equipment, and distract hospital staff from other more potentially important roles, which may stress facility and personnel resources.

Herein, we propose a multidisciplinary care framework (Table 1) for the aging patient with breast cancer in efforts to maintain optimal care while limiting undue risk from SARS-CoV-2 during this extended epidemic. Although data on this virus and its impact on the geriatric oncology population remain sparse, the treatment considerations discussed here are derived from the limited data and position papers on management of older adults with breast cancer and aging. These recommendations remain relevant as we navigate the "new normal" for the approximately 30% of breast cancer patients aged 70 years and

Table 1. General considerations for the patient aged 70 years and older with breast cancer during the COVID-19 pandemic and beyond[a]

Disease setting	Treatment considerations[a]
Lower-risk HR+ HER2- cancers	• Consider options for (a) primary hormonal therapy; (b) BCS and hormonal therapy; or (c) BCS, radiation, and hormonal therapy • Consider hypofractionation whenever possible if radiation is administered • Avoid sentinel lymph node biopsies for those with low-risk disease • Consider neoadjuvant hormonal therapy in any patient with locally advanced disease and/or those awaiting breast surgery
Higher-risk HR+HER2- disease	• Use genomic profile testing to confirm chemotherapy benefit • Select and modify any neo/adjuvant chemotherapy regimens and supportive medications to minimize immunosuppression[b]
Triple-negative disease	• Limit use of neo/adjuvant chemotherapy in small tumors • Select and modify any neo/adjuvant chemotherapy regimens and supportive medications to minimize immunosuppression[b]
HER2+ disease	• Limit use of neo/adjuvant chemotherapy in small tumors • Use hormonal therapy when also HR+ • Select and modify any neo/adjuvant chemotherapy regimens and supportive medications to minimize immunosuppression[b] • Consider T-DM1, T-DM1 plus pertuzumab, or weekly paclitaxel-trastuzumab (+/-) pertuzumab if neo/adjuvant treatment required • Consider cessation of trastuzumab before 1 year when appropriate or use of subcutaneous administration to limit infusion time
Metastatic disease	• Discuss goals of care • Consider postponement of or dose-reduced cyclin-dependent kinase 4,6 inhibition until COVID-19 exposure risks decline • Consider oral therapy when appropriate (ie, capecitabine) • Select and modify any neo/adjuvant chemotherapy regimens and supportive medications to minimize immunosuppression[b]

aAlways consider patient priorities, preferences, concerns, competing comorbidity, life expectancy, frailty, and functional status in decision making; discuss anticipated benefits and harms of treatments. BCS = breat conservation; HR+ = hormone-receptor-positive; (T-DM1) = ado-trastuzumab emtansine.
bSuch as limiting steroid use, using growth factor, avoiding anthracyclines, and modifying sequence of therapy.

older who are diagnosed in the United States annually and for the thousands of older patients living with recurrent and/or metastatic disease. As we begin to emerge from the acute effects of the COVID-19 pandemic on the care of patients with cancer, we need to reflect on what aspects of COVID-19–induced decision making and treatment considerations are worth sustaining into the future.

Of note, although we often refer to aged 70 years and older as a potential threshold for older patients throughout this manuscript based on randomized controlled trials (RCTs) that often include this age group in eligibility, our suggestions are relevant for any patient with clinically significant comorbidity, poor functional status, or advanced functional age, regardless of chronological age (6,7). Treatments for patients of all ages should be considered in the context of their underlying risk for cancer recurrence and therapy options, anticipated life expectancy, frailty, and competing risk of contracting and developing severe COVID-19. Unfortunately, we have limited data, apart from age, of the full spectrum of illnesses that place a woman at increased risk of complications.

Hormone Receptor-Positive (HR+) HER2- Tumors

Approximately 80% of women aged 70 years and older have HR+HER2- disease. Fortunately, older patients—especially those aged 70 years and older—with lower-risk HR+ disease have several treatment options, given the long-term data that exist from multiple RCTs in the local therapy setting. These minimization-of-therapy practices include the omission of sentinel lymph node biopsy (8–10), radiation (11–16), or even surgery in the setting of hormonal therapy administration (17–21). Although local treatment omission has historically had variable uptake in clinical practice (22–25), these strategies should be reconsidered in the COVID-19 era and beyond because they do not compromise outcomes. In particular, the data for radiation omission are robust and can likely be extrapolated to those with larger tumors after multidisciplinary discussion. However, if radiation is pursued after breast conservation or mastectomy, hypofractionated schedules are encouraged whenever appropriate (26–28), and it may be reasonable to delay the initiation of adjuvant radiotherapy up to 12–20 weeks from the time of surgery and 12 weeks from last chemotherapy (29).

To reduce resource utilization, including staffing, equipment, and supplies, in the operating room and to minimize risks of hospital-acquired COVID-19 infection, initiation of preoperative hormonal therapy and delay of surgery are routinely being adopted nationwide, particularly in regions of high SARS-CoV-2 prevalence. Preoperative hormonal therapy can be initiated not only in locally advanced disease, where up to 6 months of therapy is considered within standard of care, but also in the setting of early-stage disease. Primary hormonal therapy in the setting of low-risk disease and in lieu of surgery as the initial treatment also remains an option for older patients and has demonstrated efficacy in multiple prospective, randomized studies for patients aged 70 years and older (17–21). Hormonal therapy, in general, provides a unique opportunity to defer

further decision making on surgery (and other adjuvant care) without compromising immunity and can be routinely explored as upfront therapy while SARS-CoV-2 concerns are high. While patients receive preoperative therapy, physical exams and/or breast imaging should continue but can happen at more extended intervals, such as every 2–3 months, and compliance with treatment should be assessed. As hospitals begin to reopen their operating rooms because of declining numbers of patients with COVID-19, risks for infection will remain on the forefront, and queues for surgical care will be an intermittent reality.

In general, the use of neoadjuvant or adjuvant chemotherapy in the older patient with HR+HER2- disease should be reserved for the patients with the highest-risk cancers, given the anticipated traditional and COVID-19–related risks and limited-to-modest treatment benefit for the vast majority of patients. If chemotherapy is being considered, we strongly suggest use of genomic profile testing such as Oncotype DX. This can be informative at the time of biopsy if preoperative therapy is being considered, even in node-positive disease (30,31), to ensure clinical benefit. We suggest an Oncotype score of greater than 30 as a potential threshold to consider chemotherapy given the lack of clearly defined benefits for older patients with scores of 26–30. In the preoperative setting, hormonal therapy can be initiated even if chemotherapy is later desired, once COVID-19 risks decline. If chemotherapy is pursued postoperatively and concerns for COVID-19 remain high, postponing treatment initiation can be considered, given that associations of chemotherapy delay and detrimental outcomes are not present for most HR+HER2- cancers (32–34).

Although chemotherapy regimens should be individualized, general strategies can be applied to limit myelosuppression, minimize visit frequency, and avoid the need for anthracyclines and steroids. We also suggest universal use of growth factor support to minimize myelosuppression, febrile neutropenia, and hospitalization risk. Standard regimens such as docetaxel and cyclophosphamide (TC) are generally preferred. Alternatively, a modified TC regimen (35–38)—currently being explored in a clinical trial for patients aged 70 years and older (NCT03858322) with use of paclitaxel (as an alternative to docetaxel) plus cyclophosphamide—may also be an option. It is noteworthy that in the Anthracyclines in Early Breast Cancer trial, standard TC × 6 cycles was equivalent to anthracycline-taxane–based regimens except when nodal disease burden was high (39). In one small study (40), dose-dense cyclophosphamide-methotrexate-fluorouracil with growth factor support has also emerged as a potential option for patients who need chemotherapy because of the lack of severe neutropenia.

In patients with the highest-risk breast cancers, where an anthracycline is felt to be an important component of therapy, one can also consider sequential therapy as per the Cancer and Leukemia Group B 9741 trial (41). In this study, the sequential regimen was as efficacious as dose-dense combination therapy and included every 2-week doxorubicin (A) × 4 cycles followed by paclitaxel (T) × 4 cycles, followed by cyclophosphamide (C) with growth factor support. However, in this case, one might consider postponement of the anthracycline portion of therapy until after the T-C or T alone (ie, upfront paclitaxel) to minimize the immediate myelosuppression and cardiomyopathy risk.

Triple-Negative (TN) Tumors

Treatment modifications in the minority (10%) of older women who have TN breast cancer may be less feasible and will require more extensive multidisciplinary collaboration. For those with clinical stage I or even stage II disease who are breast-conserving candidates at baseline, a multidisciplinary team should determine the optimal sequence of surgical, radiation, and systemic treatments. If a postponement in surgery is necessary or in the setting of locally advanced disease, one can consider chemotherapy with one of the regimens previously discussed. Weekly carboplatin-paclitaxel with deferment or omission of anthracycline is also a chemotherapeutic option in the preoperative or postoperative setting (42,43). However, we recommend against chemotherapy for the majority of patients with stage I TN disease, given the small absolute benefits and the added risk for complications if SARS-CoV-2 infection occurs. Evidence does not support the omission of procedures such as radiation and node assessment even in lower-risk TN disease, although multidisciplinary conversations on the anticipated risks and benefits of these procedures and the associated exposures will help determine the best course of action.

HER2+ Tumors

In the approximately 10% of older breast cancer patients who are diagnosed with HER2+ tumors, there are also treatment modifications to consider. Because half of these patients will also have HR+ disease, hormonal therapy remains a treatment on its own in the setting of small tumors and frailty. Hormonal therapy could also be considered in combination with HER2-directed therapy without chemotherapy. In the case of HR-HER2+ disease where HER2-directed therapy is desired, preoperative and postoperative treatment with nonmyelosuppressive agents may be preferred at this time. Evidence-based, efficacious options include ado-trastuzumab emtansine (T-DM1) (44) or T-DM1 plus pertuzumab, which is well tolerated and can be highly effective, particularly in patients with HER2 immunohistochemistry 3+ disease (45).

Although the RESPECT trial evaluated adjuvant trastuzumab monotherapy vs trastuzumab plus physician choice chemotherapy in patients 70–80 years of age (46), this study demonstrated a nonstatistically significant, worse disease-free survival for the trastuzumab-only arm. This trial did not include a no-treatment arm to ascertain the impact of trastuzumab, and thus its applicability in this setting is limited. We also recommend avoidance or postponement of anthracyclines or carboplatin-based regimens. Other ways of minimizing exposure to SARS-CoV-2 for those on the maintenance portion of trastuzumab is subcutaneous trastuzumab or the consideration of cessation of maintenance therapy after 6 months given the limited differences in outcomes for those receiving 6 vs 12 months of trastuzumab in 2 large RCTs (47,48). Omission of radiation in selected situations for those receiving anti-HER2 therapy may also be considered given the low locoregional risk for these patients.

Metastatic Disease

As always, the degree of palliation in the metastatic disease setting should be dictated by the symptoms, disease burden, and disease subtype. In the HR+ setting when symptom burden is low, oral hormonal monotherapy is appropriate, with deferment of cyclin-dependent kinase 4,6 inhibition in most patients until the risks from COVID-19 are lowered. However, continuation of previously beneficial and well-tolerated therapy of any kind is reasonable but perhaps with decreased frequency of visits, more virtual visits, and/or dose reductions or cessation of cyclin-dependent kinase 4,6 inhibitors in the short term. When

chemotherapy is necessary across all disease subtypes, selection of regimens with consideration of comorbidity, frailty, life expectancy, toxicity, patient preference, and quality of life is warranted, with preferences for lower-intensity oral regimens such as capecitabine. Upfront dose reductions in noncurative intent settings can also be considered to minimize toxicity in older patients. In the HER2+ disease setting, there are options to modify treatment schedules, avoid myelosuppressive chemotherapy, or implement drug holidays, particularly for those with long-standing and well-controlled disease. Treatment decisions in the metastatic setting will always remain highly individualized, although the threat of COVID-19 in this vulnerable population should encourage discussions—which typically take place at a later time—on goals of care, completion of advance directives, avoidance of hospitalizations whenever necessary, and hospice when appropriate.

Follow-up and Surveillance

Given the absence of proven benefit for annual, routine mammography in the aging patient with comorbidity (49) and the arbitrary intervals for follow-up care and examination, all routine follow-up and breast imaging in the absence of symptoms can be deferred for the time being to minimize unnecessary patient and staff exposures (50). We anticipate this postponement of breast imaging will spur discussions on the limited utility of surveillance mammography that reach beyond the pandemic, with an increased awareness that routine mammography has low value in patients with limited life expectancy and competing comorbidity.

Studying the Impact of COVID-19 on Older Patients With Cancer

Understanding the impact of COVID-19 on older adults with cancer will require coordinated multicenter collaboration to study both infected and uninfected aging patients who were treated during the pandemic. Decision making, treatment patterns, and outcomes (cancer related and COVID-19 related) will need to be studied, and a consensus on the treatment modifications we want to take forward into the post–COVID-19 era will need to be reached. There will be important details to analyze in these data, particularly for those infected with SARS-CoV-2, including the types of treatments patients were receiving and how community-dwelling and hospitalized patients fared. Some relevant efforts are now underway, led in part by the Cancer and Aging Research Group and others, which will work to establish an evidence base in this context. However, more efforts are needed to integrate geriatric-guided approaches in ongoing efforts to understand the clinical and biological implications of SARS-CoV-2 infections in older adults with cancer.

In summary, the COVID-19 pandemic has reinforced the preexisting importance of the multidisciplinary, patient-centered approaches when caring for aging patients with breast cancer. In addition, treatment decisions must now consider our public health threats, including the health of medical staff and adequacy of resources. Even as the numbers of COVID-19 cases decline in some regions, we are now facing a new normal for older adults who remain at a protracted risk for infection. Efforts to minimize immunosuppression and potential COVID-19 exposures will remain crucial, as will the lessons we have learned with regard to resource allocation and patient preferences.

As always, there is power and comfort in reassurance and clear messaging to patients and their loved ones when creating treatment plans, advising them of our concerns, and including them in the conversation. If patients understand that we are trying not to compromise benefits when we modify treatment plans, they will appreciate our goals to keep them home, safe, well, socially distanced, and with as intact an immunity as possible. In the end, there are many lessons to take with us into the post–COVID-19 era. If nothing else, as an oncology workforce, we will be stronger, more agile, adaptable, appreciative, and thoughtful in our approach to care than ever before.

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