Special Considerations in the Management of Older Adult Patients With Metastatic Breast Cancer

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A majority of new cancer cases occur in older adults (aged 65 years and older); however, older adult patients often are underrepresented in clinical trials. Because of this, sufficient evidence is lacking for the creation of treatment guidelines for older adult patients. Evidence has shown that many therapeutic agents are effective in both older and younger adult patients. Although efficacy outcomes may be similar, safety profiles may differ by age because of inherent differences in drug metabolism or other reasons. The underrepresentation of older adult patients in clinical trials is explored in this article, along with the current recommendations for treating older adult patients with metastatic breast cancer (MBC). In addition, current evidence from clinical trials and subanalyses of older adult patients with MBC are discussed. Finally, nursing considerations for the management of older adult patients with MBC are provided.

The number of older adult patients (aged 65 years and older) with cancer is rising as the population of the United States ages (Smith, Smith, Hurria, Hortobagyi, & Buchholz, 2009). In a study by Smith et al. (2009), the total incidence of cancer was projected to increase by 45% overall by the year 2030. In addition, by the year 2030, an estimated 70% of all cancers will be diagnosed in older adults (Smith et al., 2009). Aside from female gender, increasing age is the most important risk factor for breast cancer (American Cancer Society, 2012b). About 43% of all new cases of invasive breast cancer were diagnosed in women aged 65 years or older in 2011 (American Cancer Society, 2012a). Although treatment of metastatic breast cancer (MBC) has improved since the early 2000s, meaningful improvements in treatment strategies have not been observed for older adult patients (Tahir, Robinson, & Stotter, 2011). In addition, many older adult patients are undertreated, and some may not be treated at all (Manders et al., 2006). The lack of meaningful improvements in treatment strategies and undertreatment of older adult patients have led to a serious impact on survival outcomes in this patient population (Bastiaannet et al., 2010; Davis, Iyer, & Candrilli, 2011). The five-year relative survival rate is more than 20% for all patients with MBC (Howlader et al., 2012); however, studies have shown that the five-year survival rate is 20% or less for patients aged 65 years or older (Bastiaannet et al., 2010; Davis et al., 2011). Identifying optimal treatment strategies for older adult patients with MBC is, and will remain, of great importance. Unfortunately, many challenges exist in treating older adult patients. In this article, in addition to exploring these challenges, recommendations for treating older adult patients with MBC, clinical outcomes in select trials of older adult patients with MBC, and considerations for nursing practice are discussed.

Treatment Challenges

Older adult patients are a heterogeneous population with multiple factors that can affect the efficacy and safety of chemotherapy. Aging is associated with changes to most body systems—including endocrine, cardiac, gastrointestinal, renal, hepatic, pulmonary, hematologic, immune, musculoskeletal, and neurologic systems—that can impact the efficacy of cancer treatment and increase the risk of toxicities (Sawhney, Sehl, & Naem, 2005; Sehl, Sawhney, & Naem, 2005). Renal function changes are the most significant changes in older adults...
Physiologic changes, comorbidities, and polypharmacy are major factors affecting the treatment of older adult patients with MBC; however, a number of other factors also exist. In general, in the older adult population, limited clinical data exist on the efficacy and safety of many therapeutics. The main reason is that older adult patients are underrepresented in a large number of clinical trials (Debled, Bellera, Donamaria, & Soubeynan, 2011). A survey of 156 providers who treated patients with breast cancer indicated several reasons for that underrepresentation (Kornblith et al., 2002). One reason, as described previously, is that older adult patients may have significant comorbid conditions that could affect treatment response. Another reason is that older adult patients may have difficulty comprehending the requirements of a trial, leading to poor adherence. Providers also are concerned about treatment-related toxicities in older adult patients. In addition, older adult patients often do not meet inclusion criteria for trials. Older adult patients who are enrolled in clinical trials tend to be healthier, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 (see Table 1 for ECOG PS definitions), making it difficult to apply the results of older adult women with breast cancer to the general population (Debled et al., 2011). Many providers may be unaware of open or ongoing clinical trials that are enrolling older adult patients (Kornblith et al., 2002). A study by Siminoff, Zhang, Colabianchi, Sturm, and Shen (2000) found that providers were significantly more likely to offer clinical trials to patients when they were aware of an open trial for which the patient was eligible. In addition, older adult patients may not want to participate in clinical trials because they may not be interested in aggressive treatment or may not want to feel like a test subject (Kornblith et al., 2002).

Providers rely on guidelines and recommendations to formulate the appropriate treatment for their patients. Evidence-based recommendations for older adult patients with MBC are limited because of the underrepresentation of this patient population in trials; therefore, providers do not have a strong basis from which to form opinions on appropriate therapeutic options for these patients (Biganzoli et al., 2012). In addition, many older adult patients do not receive optimal treatment for breast cancer because of therapeutic nihilism, both on the part of the treating provider and the patient (Raghavan & Suh, 2006). In essence, the provider and/or patient may feel that treatment may make little difference in extending an older adult patient’s life because of his or her advanced age, and that the benefit may not outweigh the potential side effects. Providers may underestimate a patient’s life expectancy, leading to ineffective or,

TABLE 1. Eastern Cooperative Oncology Group Performance Status Definitions

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
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<tr>
<td>0</td>
<td>Fully active; able to carry on all predisease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
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Treatment Recommendations

Studies that do report older adult data often are retrospective subgroup analyses, not large prospective trials (Biganzoli et al., 2012). Therefore, treatment often is based on extrapolation of study results from small analyses or from trials of younger adult patients (Biganzoli et al., 2012). The lack of clinical trial data in older women with breast cancer has limited the comprehensiveness of evidence-based treatment recommendations and guidelines (Biganzoli et al., 2012). However, recommendations for the management of older adult patients with breast cancer have begun to take shape. In 2007, the Société Internationale d’Oncologie Gériatrique (SIOG) published recommendations for the management of older adult patients with breast cancer (Wildiers et al., 2007). The recommendations were expanded in 2010 and updated in 2012 by a multidisciplinary task force created by SIOG and the European Society of Breast Cancer Specialists (Biganzoli et al., 2012). General recommendations provided by the task force were that all management decisions for older adult patients with breast cancer should consider physiologic (not chronologic) age, life expectancy, potential risks versus absolute benefits, treatment tolerance, patient preference, and potential barriers to treatment. With regard to chemotherapy for older adult patients with MBC, hormone therapy was recommended as the treatment of choice for those patients with estrogen receptor (ER)-positive MBC, whereas single-agent and combination chemotherapy were indicated for patients with ER-negative, hormone refractory, or rapidly progressing disease. The recommendations also stated that chemotherapy agents with more tolerable safety profiles, such as taxanes, capecitabine, and vinorelbine, were preferable in the management of older adult patients with MBC. In addition, the recommendations mentioned that, in older adult patients with MBC, bevacizumab has demonstrated a benefit with regard to progression-free survival (PFS); however, a limited overall survival (OS) benefit has been observed (Biganzoli et al., 2012; O’Shaughnessy et al., 2010). Although data are limited, human epidermal growth factor receptor 2 (HER2)-targeted therapies, such as trastuzumab and lapatinib, were found to be equally effective in older and younger adult patients with MBC (Biganzoli et al., 2012; Brunello et al., 2008; GlaxoSmithKline, 2012). The SIOG and the European Society of Breast Cancer Specialists task force placed a strong emphasis on geriatric assessments, particularly the comprehensive geriatric assessment (CGA) (Biganzoli et al., 2012). The CGA is an individually tailored, multiple domain assessment that requires an interdisciplinary team of healthcare providers including oncologists, geriatricians, physical therapists, social workers, and nurses (Bernabei, Venturiero, Tarstiani, & Gambassi, 2000). Figure 1 shows the major domains of the CGA. Although implementation of the CGA is an ambitious task because of its extensive nature, the task force pointed out that strong evidence indicated that use of the CGA could improve survival, quality of life, tolerability, and compliance (Biganzoli et al., 2012). The overarching theme of the 2012 recommendations was that chronologic age should not be the only factor considered when managing the care of the older adult population. Instead, many factors need to be considered when treatment decisions are made for this population. Each patient should be evaluated individually by careful examination of functional status, cognitive status, comorbidities, nutritional status, treatment tolerance, and patient preferences, including beliefs and values. In addition, barriers to treatment should be identified, each patient should be carefully followed, and toxicities should be identified and appropriately managed.

Clinical Trials

From the review of several studies aimed at treating older adult patients with MBC, as well as older adult subanalyses of clinical trials, the evidence shows that many treatments which are effective in younger patients also are effective in this population.

Single-Agent Taxanes

Several phase II trials have assessed the activity of single-agent taxanes in the older adult population, including one post-hoc analysis of all three taxanes (Aapro, Tjulandin, Bhar, & Gradishar, 2011) (see Table 2). In 2005, a phase II study examined weekly paclitaxel as first-line treatment in 48 older adult patients with advanced breast cancer (Del Mastro et al., 2005). In that study, patients aged 70 years and older with stage III or IV breast cancer were treated with weekly paclitaxel 80 mg/ m². The median age of patients was 74 years, and most patients had an ECOG PS of 0 or 1. For all patients, the median OS was 35.8 months. The most common comorbidities were hypertension (63%), arthritis (37%), and osteoporosis (29%). The overall response rate (ORR) for the 32 patients with stage IV disease was 44%. All patients were evaluable for safety. Of the AEs reported, most were grade 1 or 2, and the rate of each severe (grade 3 or
4) AE reported, including neutropenia, anemia, hypersensitivity reaction, fatigue, and neuropathy, was less than 10%. Severe cardiovascular complications did occur in the study, leading to death in two cases, and unacceptable toxicities within the first four cycles occurred in five other patients. A study by ten Tije et al. (2004) reported similar findings from another phase II study of weekly paclitaxel 80 mg/m² as first-line treatment for older adult patients with MBC. In that study, a dose increase to 90 mg/m² was allowed in the absence of unacceptable toxicity. The ten Tije et al. (2004) study enrolled 26 patients aged 70 years or older with stage IV hormone-refractory breast cancer. The median age of patients was 77 years, and most patients had a World Health Organization (WHO) PS of 0 or 1 (using the WHO scale, sensory and motor signs and symptoms are combined into one scale, rated from 0–4, with higher scores meaning worse neuropathy). The ORR in the 23 patients available for response assessment was 38%, and all were partial responses. In the 25 patients assessable for safety, most of the AEs reported were grade 1 and 2; however, grade 3 neutropenia and anemia occurred in 12% of patients. Grade 3 hypersensitivity reactions, fatigue, neuropathy, and vomiting each occurred in 4% of patients. The mentioned studies demonstrated that weekly paclitaxel was efficacious and had a tolerable safety profile in older adult patients with MBC.

Docetaxel also has been investigated in several phase II studies of older adult patients with MBC (D’hondt et al., 2004; Hainsworth et al., 2001). Hainsworth et al. (2001) treated 41 patients who were either older than aged 65 years or were considered to be poor candidates for combination therapy (i.e., comorbidities or poor tolerance for previous chemotherapy regimens). Docetaxel was given at a dose of 36 mg/m² weekly. Patients in that study ranged in age from 50–88 years, with a median age of 74 years; most patients had an ECOG PS of 0 or 1 and had visceral metastases. The ORR in the 36 patients available for response was 36%. All patients were assessable for safety, and the most common severe AEs were fatigue and asthenia (20%), diarrhea (10%), nausea and vomiting (7%), and peripheral edema (7%). Severe hematologic events were not common, with grade 3 or 4 anemia and leukopenia occurring in 4% and 5% of patients, respectively. D’hondt et al. (2004) performed a similar phase II study of docetaxel in 47 patients with MBC who were aged 70 years or older or ineligible for standard every-three-weeks docetaxel because of poor hematologic reserves, impaired liver function, intolerance to previous taxane therapy, or any combination of those reasons. Docetaxel was given at 36 mg/m² weekly. Patients ranged in age from 43–82 years, with a median age of 63 years, and most patients had a WHO PS of 1 or 2. Of the 37 patients evaluable for response, the ORR was 30%; of the patients for whom being aged 70 years or older was the only risk factor, the ORR was 7% (4 of the 10 evaluable patients had a partial response). In patients whose only risk factor was age (70 years or older, n = 11), one patient with hematologic abnormalities at baseline experienced grade 4 neutropenia, but no grade 3 AEs were reported. Grade 2 fluid retention and fatigue were reported in 18% of patients in this subgroup. The two studies demonstrated that docetaxel was effective and tolerable in older adult patients with MBC.

Beuselinck et al. (2010) compared weekly docetaxel and paclitaxel in a randomized phase II study of older adult or frail
patients with MBC. Docetaxel was given at a dose of 36 mg/m² and paclitaxel was given at 80 mg/m². Older adult patients in this study were defined as aged 70 years or older, and frail patients were those with hematologic issues, liver function abnormalities, and intolerance to prior every-three-weeks taxanes. In this study, 12 and 16 patients aged 70 years or older received paclitaxel and docetaxel, respectively. In the overall population (N = 70), 57 of the patients (81%) had an ECOG PS of 0 or 1. All older adult patients receiving paclitaxel and docetaxel who were included in this study were assessable for response, and the ORRs were 50% and 25%, respectively (all partial responses); for patients younger than 70 years (42 assessable), no difference was observed between the two taxanes in terms of ORR. AEs were reported only for the overall population (assessable patients: n = 37 for docetaxel, n = 33 for paclitaxel). The most common grade 3 or 4 AEs were neutropenia (20%), stomatitis (16%), and infection (11%) in the docetaxel arm and neutropenia (45%), anemia (21%), and infection (15%) in the paclitaxel arm. A greater percentage of patients discontinued treatment because of toxicities in the docetaxel arm versus the paclitaxel arm (45% versus 36%). The most common reasons for treatment discontinuation were fluid retention, edema, and pleural effusion in the docetaxel arm and sensory neuropathy in the paclitaxel arm. Paclitaxel produced a greater percentage of grade 3 or 4 neutropenia compared with docetaxel (45% versus 20%), as well as anemia (21% versus 5%), thrombocytopenia (12% versus 3%), and febrile neutropenia (6% versus 0%). Sensory neuropathy of any grade occurred in 57% and 46% of patients receiving paclitaxel and docetaxel, respectively. Although differences in the efficacy and safety profiles of paclitaxel and docetaxel were observed, the authors concluded that weekly schedules of these taxanes were valid options for older adult patients with MBC.

A post-hoc analysis by Aapro et al. (2011) compared the safety and efficacy of nab-paclitaxel versus weekly solvent-based paclitaxel and docetaxel in 114 older adult (aged 65 years or older) patients with MBC from two earlier trials (Gradishar et al., 2005, 2009). In the phase II trial versus docetaxel, in the older adult population, nab-paclitaxel was given at 100 mg/m² (n = 14) or 150 mg/m² (n = 10) weekly or 300 mg/m² every three weeks (n = 9), and docetaxel was given at 100 mg/m² (n = 19) every three weeks (Gradishar et al., 2009). In the phase III trial versus solvent-based paclitaxel, in the older adult population, nab-paclitaxel was given at 260 mg/m² (n = 30) every three weeks and solvent-based paclitaxel was given at 175 mg/m² (n = 32) every three weeks (Gradishar et al., 2005). The median age of patients included in the analysis was 69 years, and most patients had an ECOG PS of 0 or 1 (Aapro et al., 2011). In addition, in the phase III trial of nab-paclitaxel versus solvent-based paclitaxel, patients could have received prior chemotherapy for metastatic disease, whereas those in the phase II trial comparing nab-paclitaxel versus docetaxel did not receive prior chemotherapy (Gradishar et al., 2005, 2009). With the exception of the 300 mg/m² dose, most doses of nab-paclitaxel resulted in higher ORRs compared with either of the other taxanes in their respective trials (Gradishar et al., 2005, 2009). The analysis also showed that weekly nab-paclitaxel dosing resulted in higher response rates compared with the every-three-weeks schedule in older adult patients with MBC (Aapro et al., 2011). In older adult patients, nab-paclitaxel 260 mg/m² resulted in a longer median PFS and OS compared with solvent-based paclitaxel (Aapro et al., 2011). nab-Paclitaxel 150 mg/m² resulted in an approximately 10-month longer median PFS than docetaxel; however, median OS was similar among all doses of nab-paclitaxel and docetaxel (Gradishar et al., 2009). In both studies, the incidence of grade 4 neutropenia was lower with all doses of nab-paclitaxel compared with the other taxanes (Gradishar et al., 2005, 2009). Grade 3 sensory neuropathy also was generally lower in the every-three-weeks nab-paclitaxel arm compared with docetaxel and the weekly nab-paclitaxel arms (Gradishar et al., 2009). The authors concluded that the tolerability profiles of the older adult patients in this analysis were consistent with those for the overall population (Aapro et al., 2011; Gradishar et al., 2005, 2009).

Combination Studies

Because of the potential toxicity and limited survival gain, few combination studies have been performed in this patient population (Biganzoli et al., 2012) (see Table 3). Hess et al. (2007) reported the results of a phase II trial of capecitabine plus vinorelbine as first-line treatment in older adult patients (aged 65 years or older) with MBC. In this study, vinorelbine was given at 20 mg/m² on days 1 and 8 of a three-week cycle and capecitabine was given at 1,000 or 1,250 mg/m² daily for two weeks in patients with or without bone involvement, respectively. The study enrolled 47 patients with bone involvement and 23 patients without bone involvement, with a median age of 72 and 75 years, respectively. Most patients in the trial had a WHO PS of 0 or 1. Patients with (n = 45) and without (n = 21) bone involvement who were assessable for response had ORRs of 45% and 57%, respectively. All patients were assessable for safety, and the most common grade 3 or 4 hematologic toxicity was neutropenia, occurring in six and eight patients with and without bone involvement, respectively. Only one grade 4...
TABLE 3. Summary of Select Findings From Combination Studies in Older Adult Patients With Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Patient Subgroup</th>
<th>N</th>
<th>ORR (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
<th>Most Common Grade 3 or 4 Adverse Effects*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dong et al., 2012</td>
<td>Gemcitabine with vinorelbine</td>
<td>NR</td>
<td>51</td>
<td>33</td>
<td>6.2</td>
<td>17</td>
<td>Neutropenia (26%), anemia (14%), thrombocytopenia (10%)</td>
</tr>
<tr>
<td>Hess et al., 2007</td>
<td>Capecitabine with vinorelbine</td>
<td>Bone metastases</td>
<td>47</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Neutropenia (6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No bone metastases</td>
<td>23</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Neutropenia (17%), asthenia (13%)</td>
</tr>
</tbody>
</table>

*Adverse effects occurring in about 10% of patients or more
NR—not reported; ORR—overall response rate; OS—overall survival; PFS—progression-free survival

nonhematologic toxicity was reported—one case of nausea in a patient without bone involvement. Other key grade 3 nonhematologic AEs reported in patients with and without bone involvement were diarrhea (4% each) and asthenia (2% versus 13%). Significant changes in quality-of-life scores (positive or negative) were not observed in either group. The authors concluded that the combination of vinorelbine and capecitabine was tolerable and effective and that the tolerability of the combination was evidenced by the low incidence of severe AEs and the fact that the quality-of-life indicators did not worsen.

Results from a phase II trial by Dong, Wang, Li, Cui, and Guo (2012) of gemcitabine in combination with vinorelbine in older adult patients with MBC were reported. In the study, gemcitabine was given at 1,000 mg/m² and vinorelbine was given at 25 mg/m² on days 1 and 8 of a three-week cycle. Fifty-one patients with a median age of 73 years were enrolled, and a majority of patients had an ECOG PS of 0 or 1. Most patients received the combination as first-line therapy (55%), but some received it as second line or greater (45%). Of the 48 evaluable patients, the response rate was 33%. At a median follow-up of 16.2 months, the median PFS and OS were 6.2 and 17 months, respectively. All patients were available for safety assessment, and the most common grade 3 and 4 AEs were leukopenia (27%), neutropenia (25%), anemia (14%), thrombocytopenia (10%), and fatigue (6%). The authors of the study suggested that gemcitabine plus vinorelbine was a viable alternative for the treatment of older adult patients with MBC after anthracycline and taxane therapy.

Nursing Considerations

Education of older adult patients is a key factor in providing optimal care; therefore, nurses need to develop a trusting relationship with older adult patients. Allowing extra time for talking and listening will aid in the building of that trust. Many older adult patients have decreased cognitive abilities and may have difficulty understanding the information they are told. Some older adult patients may even be afraid or confused about their treatment. Slow and careful delivery and repetition of directions or information is an important way to aid in patient understanding and reduce anxiety. In addition, some older adult patients may find it difficult to accept change; therefore, incorporating understanding a patient’s own personal beliefs and values may help to facilitate the learning process as well as aid in forming treatment regimens and management strategies. Important goals for healthcare providers when dealing with older adult patients are evaluating each patient as an individual and identifying optimal treatment strategies that balance life expectancy with treatment toxicity and quality of life. Healthcare providers should take as much time as is necessary to perform thorough examinations, which will aid in the identification and appropriate management of treatment-related toxicities in older adult patients. Older adult patients also are at risk for undertreatment of pain (Bernabei et al., 2000); one reason is that older adult patients are less likely to report pain symptoms than younger patients (Herr & Mobily, 1991). Therefore, assessment of pain using a rating tool such as a visual analog scale at every visit is important for ensuring that older adult patients are optimally treated. Treatment of MBC in the older adult is complicated and requires a multidisciplinary team approach.

Multiple members of a care team are required to manage the optimal physical, social, and psychological aspects of care. Because of that, nurses are a vital point of contact for patients, and they can help to gather and condense information from the individual areas of care, which may otherwise be too much for an older adult patient to take in. Well-informed patients will make decisions based on their own beliefs and values. Although those decisions may not always coincide with the nurse’s opinions, being a patient advocate and supporting patients’ decisions is a key role for nurses. The role of the nurse as a patient advocate also involves assisting the patient with communicating concerns to other healthcare providers. Ensuring that patients are well educated and building a trusting relationship will help patients to receive optimal care.

Conclusion

Older adult patients with MBC often are quite different than the general population, with, among other things, increased comorbidities, polypharmacy, and decreased organ function (Biganzoli et al., 2012; Debled et al., 2011; McLean & Le Couteur, 2004). Therefore, adapting and applying knowledge from clinical trials of younger adult patients is not an optimal treatment strategy. With regard to the CGA, future work should focus on developing a more user-friendly assessment aimed at nurses that could be administered in the outpatient setting—a setting that does not always offer enough time for a highly comprehensive assessment, such as the CGA. Although...
several trials and analyses have assessed the efficacy and safety of single-agent and combination chemotherapy, specifically in older adult patients with MBC, a need still exists for more trials examining treatment regimens, dosing, management strategies, tolerability, and outcomes in this patient population. A larger number of clinical trials in older adult patients with MBC will provide support for future recommendations and guidelines for the treatment of this population, which, in turn, will help to provide optimal treatment for older adult patients. Overall, formulation of a treatment plan for older adult patients should not only take into account age, but also multiple other factors including cognitive function, comorbidities, physical functioning, and beliefs. Finally, from the nursing perspective, taking time to nurture relationships with older adult patients will ultimately ensure that they receive the best care possible.

References


