Clinical Roundtable Monograph

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Effective Management of Quality of Life in Metastatic Breast Cancer

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Abstract: Quality of life is accepted as an important consideration in the management of patients with metastatic breast cancer, which remains incurable. Recent clinical trials of newer agents, such as eribulin and trastuzumab emtansine, have incorporated quality of life analyses. Quality of life is impacted by multiple patient-related, disease-related, and treatment-related factors. Therapies most beneficial for maintaining or improving quality of life include those that can effectively reduce tumor burden and tumor-related symptoms, but have toxicity profiles that are well tolerated and easily managed. Overall outcomes of patients with metastatic breast cancer improve when therapy is focused not only on the disease itself, but also on the goals of minimizing disease-related and treatment-related symptoms. A paradigm shift now reflected in major guidelines is the incorporation of palliative care strategies earlier in the course of metastatic disease management. The selection and sequence of treatments should be made in cooperation with the patient and after consideration of her particular priorities.

Sponsored by the Postgraduate Institute for Medicine

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Target Audience

This activity has been designed for all physicians, academicians, researchers, investigators, support staff, nurses, and program directors from the fields of oncology with a special interest in metastatic breast cancer.

Statement of Need/Program Overview

Despite advances in the use of targeted agents to treat metastatic breast cancer, the disease remains incurable. When managing patients with metastatic breast cancer, physicians should place an equal emphasis on survival and quality of life. Quality of life in these patients encompasses several components, such as maintaining or improving performance status and functional status, minimizing treatment side effects, and managing disease-related symptoms. Recent clinical trials of newer agents, such as eribulin and trastuzumab emtansine, have incorporated quality of life analyses. Palliative treatment, which focuses on fatigue, depression, insomnia, and pain, should be initiated at the time of diagnosis. Mounting evidence suggests that the overall outcomes of patients with metastatic breast cancer improve when therapy is focused not only on the disease itself, but also on the goal of minimizing disease-related and treatment-related symptoms.

Educational Objectives

After completing this activity, the participant should be better able to:

- Describe the quality-of-life issues faced by patients with metastatic breast cancer
- Accurately assess quality of life in metastatic breast cancer patients
- Discuss how qualify of life impacts overall health and prognosis in patients with metastatic breast cancer
- Implement strategies to maintain or improve quality of life in metastatic breast cancer patients

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Quality of Life in Patients With Metastatic Breast Cancer

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Currently, there are no curative therapies for patients with metastatic breast cancer. The primary goal of treatment is to provide palliative care. Each of the therapies used in the treatment of metastatic breast cancer has its own unique set of potential side effects, such as peripheral neuropathy and alopecia. A treatment's side effects should be mitigated by the improvement it makes in the number and severity of disease-related symptoms. Therefore, when deciding among treatment options, clinicians must consider not only traditional outcomes, such as prolonging progression-free survival and reducing tumor burden, but also maintaining the patient's quality of life.

Quality of life is influenced by disease-related, patient-related, and treatment-related factors. Patients will often experience symptoms that are related to the presence of the cancer itself, especially as the disease progresses to the metastatic stage (Table 1).[1] For example, lung metastases can cause shortness of breath, and bone metastases can result in bone pain. Depending on the bulk of the disease, patients may experience symptoms such as fatigue and loss of appetite. Psychologic issues, including anxiety and depression, can arise after a diagnosis of breast cancer. Patients may worry about whether they will continue to be functional, be able to interact with family and friends, and be able to care for themselves over time. Adverse events related to treatment may also have a significant impact on quality of life.

Table 1. Associated Symptoms of Metastatic Breast Cancer

Metastatic Site	Associated Symptoms
General	Fatigue, difficulty sleeping, depression
Bone	Pain, hypercalcemia, pathologic fracture, loss of mobility
Central nervous system (brain, leptomeningeal disease, spinal cord)	Headache, confusion, weakness, pain, seizure, altered mentation, cranial nerve palsies, speech impairment
Skin	Pain, infection, bleeding
Gastrointestinal tract (eg, liver, ascites, peritoneum)	Pain, nausea, vomiting, diarrhea, early satiety, loss of appetite, dyspnea (from ascites), jaundice, bleeding
Pulmonary	Pain, dyspnea, hemoptysis, cough
Lymph nodes	Brachial plexopathies, pain

Data from Irvin W Jr et al. *Oncologist*. 2011;16(9):1203-1214.[1]

Integrating Palliative Care

Historically, palliative care has been reserved for use toward the end of life. More recently, groups such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network have recommended that palliative care be incorporated into the management course starting from the time of the patient's initial diagnosis.[2,3] As noted in a provisional clinical opinion from ASCO, evidence now shows that the integration of palliative care into standard management—or as the main focus of care—results in better patient outcomes, including improvements in symptoms and quality of life, as well as increased patient satisfaction and reduced caregiver burden.[2]

In metastatic breast cancer, this approach would mean that palliative care is administered concomitantly with disease-targeted therapy, as these patients are in a period clinicians often consider "survivorship." As the disease continues to recur, and as the patient begins to decline in health status and deplete the therapeutic alternatives that would modify her disease, the priority becomes making her as comfortable as possible. When palliative care is considered in the management continuum, many opportunities to intervene become apparent. For example, many side effects of therapy, such as fatigue and shortness of breath, are long-lasting and persist even after the course of treatment ends. Studies conducted in patients with metastatic breast cancer and other malignancies have

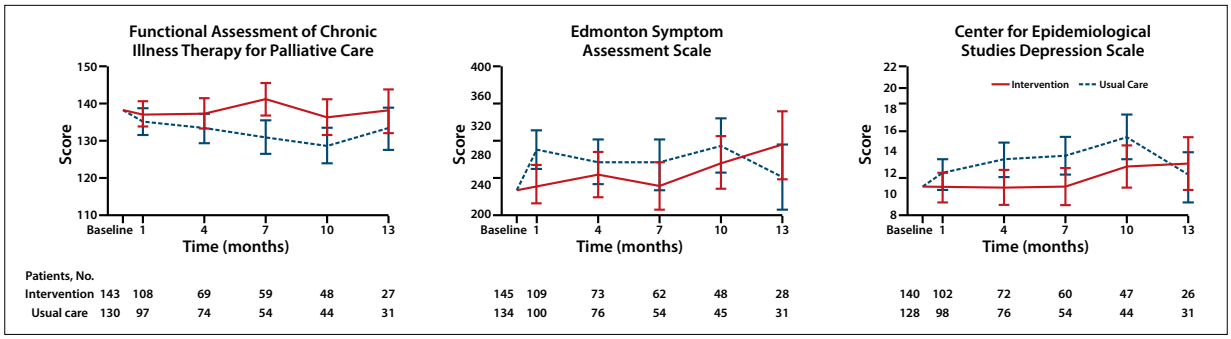

Figure 1. In the randomized controlled trial Project ENABLE II, an intensive palliative care intervention increased quality of life over standard care across a variety of scales. The range for the Functional Assessment of Chronic Illness Therapy for Palliative Care is 0 to 184, with higher scores indicating better quality of life. The Edmonton Symptom Assessment Scale ranges from 0 to 900, with higher scores indicating greater symptom intensity. The Center for Epidemiological Studies Depression Scale ranges from 0 to 60, with higher scores indicating more depressive symptoms. Each analysis was adjusted based on the respective baseline instrument score. The error bars signify the 95% confidence intervals.

ENABLE, Educate, Nurture, Advise Before Life Ends. Adapted from Bakitas M et al. *JAMA*. 2009;302(7):741-749.[5]

demonstrated that the integration of palliative care and best supportive care measures throughout treatment can improve the patient's overall sense of well-being and even prolong survival. In a nonblinded study by Temel and colleagues, 151 patients with metastatic non–small cell lung cancer were randomized to receive standard oncologic care alone or with integrated palliative care.[4] The palliative care management plan was based on factors such as physical and psychosocial symptoms, goals of care, and the patient's individual needs. The addition of early integrated palliative care was associated with a significantly better quality of life than oncologic care alone (mean scores of 98.0 vs 91.5 on the Functional Assessment of Cancer Therapy–Lung [FACT-L] scale; *P*=.03). Additionally, symptoms of depression were less common in patients who received early integrated palliative care vs those who did not (16% vs 38%; *P*=.01). The need for aggressive end-of-life care was less common in patients who received early integrated palliative care (33% vs 54%; *P*=.05). (This end-of-life care was defined as chemotherapy within 2 weeks of death, no hospice care, or admission to hospice within 3 days before death.) Importantly, the median overall survival rate was prolonged in patients who received palliative care (11.6 vs 8.9 months; *P*=.02). Studies conducted in breast cancer patients have confirmed these findings. Objective response often correlates with improvement in patient symptoms when the focus of therapy is not only to achieve disease-related improvement, such as tumor response, but also to improve symptoms and other quality-of-life indices.

Palliative care nursing is a critical component to improvement of quality of life in cancer patients. Project ENABLE (Educate, Nurture, Advise Before Life Ends) II was a randomized controlled trial that evaluated an intensive palliative care intervention administered by a palliative care advanced-practice nurse.[5] The program addressed physical and psychosocial needs as well as care coordination. Patients were randomized to receive this intervention early after a new diagnosis of an advanced cancer. This study included 322 patients, 10% of whom had breast cancer. The palliative care intervention was associated with higher quality of life (as measured on several indices; Figure 1) and mood.

Summary

Mounting evidence shows that the overall outcomes of patients with metastatic breast cancer improve when therapy is focused not only on the disease itself, but also on the goals of minimizing disease-related and treatment-related symptoms. This approach must become a central component of patient management. A focus on quality of life will help patients participate fully in their lives with family and friends, remain independent for as long as possible, and manage the inherent ups and downs of their illness.

Acknowledgment

Dr Gradishar has no real or apparent conflicts of interest to report.

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Quality of Life in Clinical Trials of Metastatic Breast Cancer

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The incorporation of quality-of-life measures into clinical trials for metastatic breast cancer has made clinicians much more conscious of the patient's perspective. The impact of this increased understanding has been profound and reminiscent of what was observed with the breast cancer screening program that was tested in the United Kingdom. Studies of screening strategies led to the establishment of a foundation for the development and organization of breast cancer screening programs. In a similar fashion, incorporation of quality-of-life measures into clinical trials is resulting in better recognition that these measures are critical to improving patient outcomes in routine clinical practice.

In a recent survey of patients with metastatic breast cancer conducted across several European countries, 67% of patients (or their caregivers) believed that life-extending treatment was worthwhile, despite its potential for accompanying side effects (Figure 2).[1] In contrast, fewer than 10% of respondents stated that they desired to live out their lives peacefully without any of the side effects of treatment. This survey also identified several areas in which patients desired more information (Figure 3). When balancing the risks and benefits of treating metastatic breast cancer, as clinicians we too must appreciate that the underlying cancer also has an adverse impact on a patient's quality of life.

Physicians do indeed want their metastatic breast cancer patients to live both longer and better, although this statement may be viewed as a cliché. Several decades ago, when the importance of quality of life was still a relatively new concept, many oncologists believed that they knew what was best for a patient and did not need to address a patient's particular symptoms and feelings. At that time, however, studies began to show that physicians were not especially good at understanding the disease from the patient's perspective. As a result, physicians began to be more open in their dialogue with metastatic breast cancer patients regarding the modest benefits that were achievable with current therapies and the lack of a curative option. In this context of limited efficacy, the challenges of balancing modest benefits against the potential side effects of therapy became an issue of much deeper discussion.

One important issue that remains to be addressed, especially in the era of rapidly developing targeted therapies, is the impact of lower-grade treatment-induced toxicities. Clinicians and clinical trials tend to focus on grade 3 or 4 adverse events, especially in regard to myelosuppression and febrile neutropenia. Often less attention is paid to grade 2 adverse events; persistent moderate fatigue, nausea, or stomatitis can, however, be quite debilitating for patients, negatively affecting their quality of life and potentially limiting the ability to continue therapy without modifying the dose or schedule of treatment. A focus on only acute grade 3 or 4 adverse events may lead clinicians to underestimate the impact of treatment on a patient's quality of life.

Assessing Quality of Life

One of the key elements to consider regarding quality of life is that it is best defined from the patient's perspective and is her own report of her experience. Therefore, the definition of a "good" quality of life will differ on an individual patient basis and will be affected by the patient's own unique situation. In clinical trials, quality of life scores are used to quantitatively evaluate these measures. Initially, quality of life was measured simply by using straightforward linear-analogue self-assessment scoring systems. This approach evolved into the use of more detailed systems, such as those incorporating the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.[2,3] These structured and validated systems are now heavily relied upon

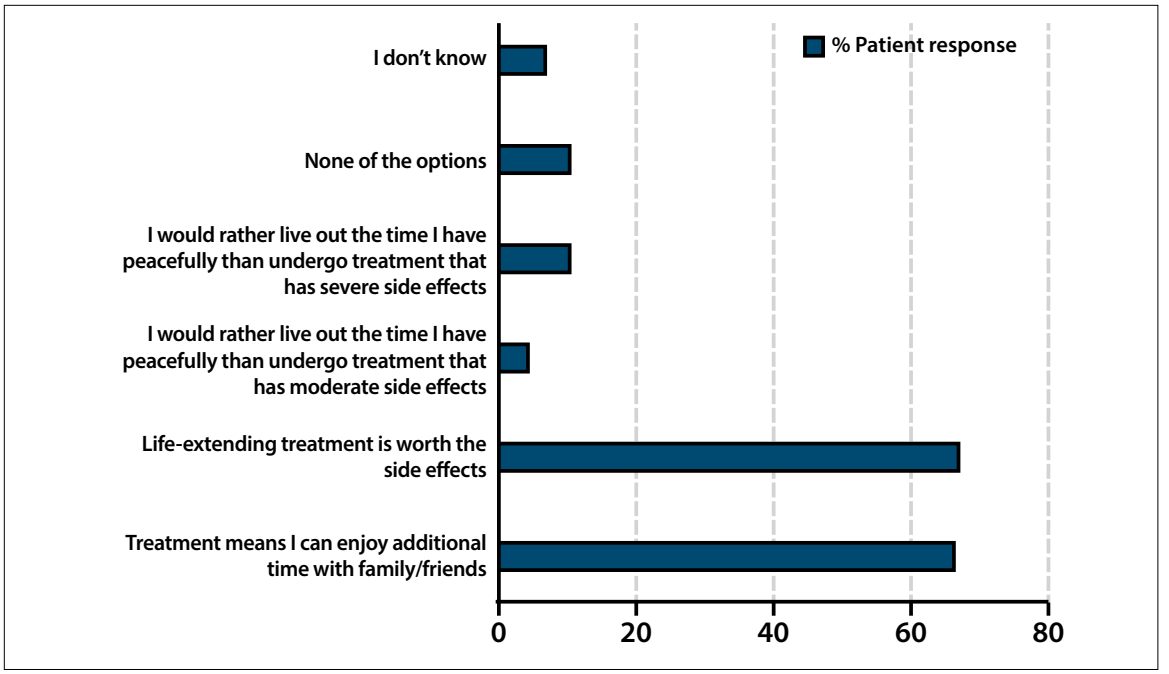

Figure 2. In a survey of patients with metastatic breast cancer conducted across several European countries, 67% of patients (or their caregivers) believed that life-extending treatment was worthwhile, despite its potential for accompanying side effects.

Adapted from Harding V et al. Br J *Cancer*. 2013;109(6):1543-1548.[1]

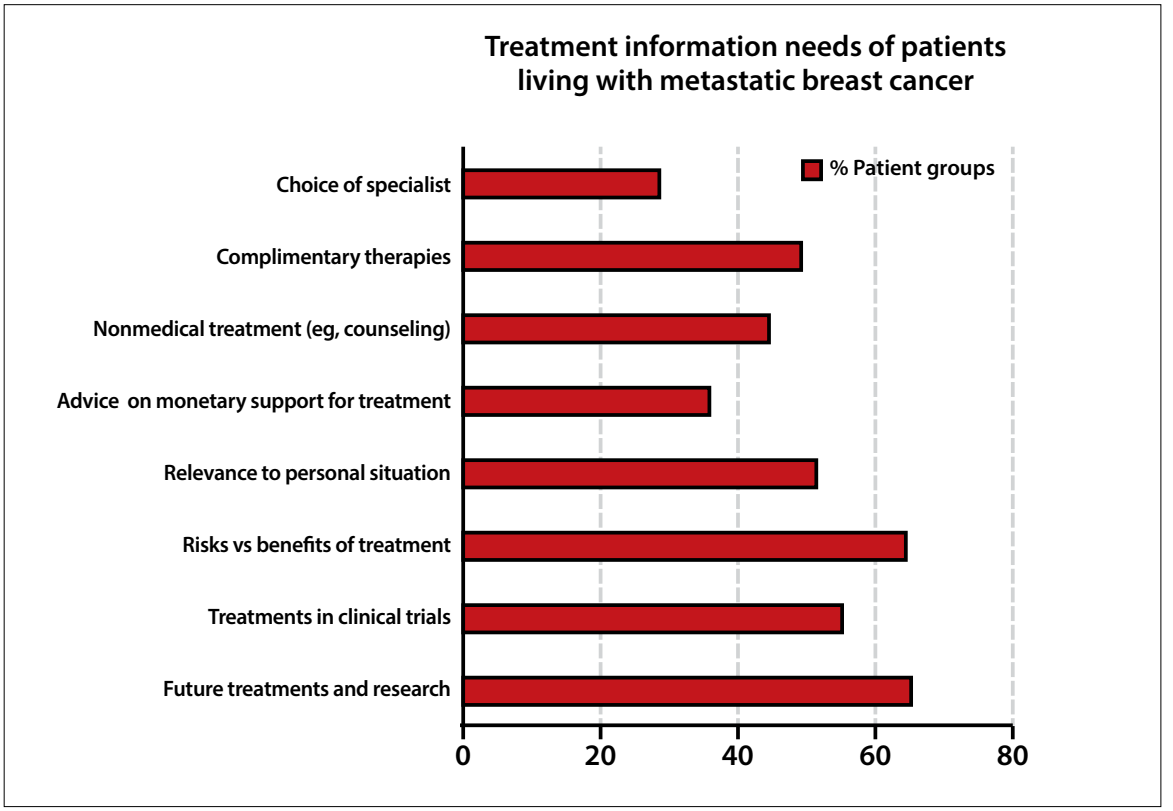

Figure 3. A survey of patients with metastatic breast cancer conducted across several European countries identified several areas in which patients desired more information.

Adapted from Harding V et al. *Br J Cancer*. 2013;109(6):1543-1548.[1]

in clinical trials. Although physicians often view these quality-of-life questionnaires as being patient-focused, it is the investigators rather than the individual patient who generate the questions that are addressed. This approach may restrict the ability of patients to report the problems most affecting them as individuals. One potential strategy to overcome this limitation, that is still being refined, is the incorporation of questionnaires that use computer touchscreens for patient-reported quality-of-life outcome measures.[4] This more interactive tool would better enable patients to indicate what they view as the most important issues they are facing.

Studies Detailing the Impact of Disease on Quality of Life

One of the most important factors affecting quality of life in patients with metastatic breast cancer is the underlying disease itself. This concept is supported by a somewhat unusual study from Greece that was published in 2007.[5] In this prospective, single-institution trial, patients with metastatic breast cancer were randomized to receive either chemotherapy or best supportive care only. Using the EORTC QLQ and the Quality of Life Questionnaire Breast 23 (QLQ-BR23), the investigators reported statistically significant improvements in quality of life among chemotherapy-treated patients. This effect was presumably achieved by the better treatment these patients received. A 1987 study by the Australian–New Zealand Breast Cancer Trials Group reached a similar conclusion.[6] Patients with metastatic breast cancer were randomized to receive either continuous or intermittent chemotherapy. Patients in the continuous arm received treatment until evidence of disease progression. In the intermittent arm, patients received an initial 3 chemotherapy cycles, with no further treatment until disease progression. Intermittent treatment was associated with a significantly shorter response rate, a significantly shorter time to disease progression, and a trend toward a shorter overall survival. For all patients, quality of life was improved during the first 3 cycles of chemotherapy. After this time, patients in the intermittent treatment arm reported worse quality-of-life scores for physical well-being, mood, and appetite. Overall quality-of-life indices as reported by patients and assessed by physicians were also reduced in the intermittent treatment arm.

Another international phase 3 clinical trial evaluated the efficacy and tolerability of the combination of capecitabine plus docetaxel compared with docetaxel alone in patients with anthracycline-treated metastatic breast cancer.[7] The combination therapy showed significant improvement in several outcomes, including median overall survival (14.5 vs 11.5 months; hazard ratio, 0.775; 95% CI, 0.634-0.947; *P*=.0126). Combination therapy was associated with higher rates of gastrointestinal side effects and hand-foot syndrome; myalgia, arthralgia, and neutropenic fever/sepsis were more common with single-agent docetaxel. Capecitabine plus docetaxel is one of few combination chemotherapy regimens that have demonstrated a significant improvement in overall survival. This combination has not, however, been widely adopted in the United States, primarily owing to oncologists' perception of its toxicity. An important observation made in this trial was that quality-of-life outcomes, which were measured on day 127, demonstrated no significant differences between the treatment groups. A separate measurement of the impact of chemotherapy-induced side effects using a systemic therapy side effects symptom scale showed no difference between the 2 treatment arms. The lack of a significant difference in quality-of-life scores is presumably attributable to a greater improvement of disease-related symptoms among patients in the more toxic combination arm.

In a randomized, multicenter, open-label, phase 3 study, docetaxel was compared with paclitaxel in patients with metastatic breast cancer following progression on an anthracycline-containing chemotherapy regimen.[8] Several clinical outcomes were improved with docetaxel compared with paclitaxel, including median overall survival (15.4 vs 12.7 months; hazard ratio, 1.41; 95%

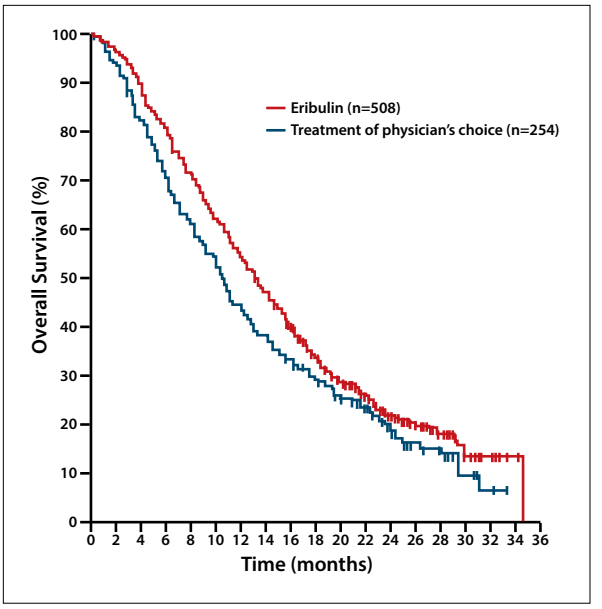

Figure 4. In an updated analysis of overall survival in the EMBRACE trial, the increase in median overall survival observed in the eribulin mesylate arm as compared with the treatment of physician's choice arm remained significant (*P*=.014).

EMBRACE, Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. Adapted from Halaven [package insert]. Woodcliff Lake, NJ: Eisai Inc; 2012.[14]

Table 2. Adverse Events in Study 301

	Eribulin (n=544) n (%)	Capecitabine (n=546) n (%)
Adverse Events	512 (94.1)	494 (90.5)
Adverse Events Reported as Treatment-Related	460 (84.6)	421 (77.1)
Serious Adverse Events	95 (17.5)	115 (21.1)
Adverse Events Reported as Treatment-Related		
Discontinuation of Treatment	31 (5.7)	34 (6.2)
Dose Reduction	169 (31.1)	171 (31.3)
Dose Delay	124 (22.8)	160 (29.3)
Fatal Adverse Events	26 (4.8)	36 (6.6)
Fatal Adverse Events Reported as Treatment-Related	5 (0.9)	4 (0.7)

Data from Kaufman PA et al. SABCS Abstract S6-6. *Cancer Res*. 2012;72(suppl 3).[15]

CI, 1.15-1.73; *P*=.03), median time to progression (5.7 vs 3.6 months; hazard ratio, 1.64; 95% CI, 1.33-2.02; *P*<.0001), and overall response rate (32% vs 25%; *P*=.10). Quality of life, which was measured using the FACT-B questionnaire, was not significantly different between the 2 treatment arms at cycle 4 or at the end of the study. Again, it can be deduced that any decrease in quality of life related to treatment side effects was counterbalanced by more effective treatment that reduced disease-related symptoms in patients receiving docetaxel.

A phase 3 trial of letrozole alone or in combination with lapatinib included an analysis of quality of life in HER-2-positive patients (n=219).[9] Quality of life was assessed with the FACT-B questionnaire at screening, every 12 weeks, and at study withdrawal. The addition of lapatinib to letrozole led to a significantly longer PFS than letrozole alone (8.2 months vs 3.0 months; *P*=.019),[10] but quality of life did not differ between the 2 treatment groups. The mean changes in quality-of-life scores were stable over time among all patients who stayed on treatment.

Quality of life was also investigated after treatment with the recently approved antibody-drug conjugate trastuzumab emtansine (T-DM1).[11] In this phase 2 study, patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic or recurrent locally advanced breast cancer were randomized to receive first-line treatment with either trastuzumab plus docetaxel or T-DM1. Median progression-free survival was significantly improved with T-DM1 as compared with trastuzumab plus docetaxel (14.2 vs 9.2 months, estimated stratified hazard ratio, 0.59; 95% CI, 0.36-0.97; *P*=.035). In this study, patients randomized to receive T-DM1 experienced fewer grade 3 or higher adverse events compared with patients randomized to receive trastuzumab plus docetaxel (46.4% vs 90.9%). Similarly, grade 4 adverse events, serious adverse events, and adverse events leading to treatment discontinuation all occurred at a reduced incidence with T-DM1. Interestingly, T-DM1–treated patients reported more favorable mean changes from baseline in FACT-B scores across all treatment cycles. The median time to a decrease of 5 or more points in the Trial Outcome Index-Physical/Functional/Breast (TOI-PFB) score was significantly prolonged in the T-DM1 arm compared with the trastuzumab plus docetaxel arm (7.5 vs 3.5 months; hazard ratio, 0.58; 95% CI, 0.36-0.92; *P*=.022), correlating with a longer time to symptom progression among these patients. This study suggests that the effect of improvement in disease-related symptoms observed with T-DM1, along with its reduced toxicity compared with trastuzumab plus docetaxel, combined to improve quality of life overall.

Analysis of quality of life was included in a phase 2 study of eribulin mesylate in women with locally advanced or metastatic breast cancer who had received previous treatment with an anthracycline, a taxane, and capecitabine. Quality of life was assessed on the first day of each treatment cycle using the EORTC QLQ-C30 questionnaire and the QLQ-BR23. Quality-of-life parameters were maintained in patients who responded to eribulin.[12] The phase 3, global, multicenter, open-label, randomized EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Treatment of Physician's Choice vs. Eribulin E7389) trial compared eribulin with a treatment of the physician's choice in 762 women with heavily pretreated locally recurrent or metastatic breast cancer.[13] In the treatment of physician's choice arm, the vast majority of patients (96%) received chemotherapy, including vinorelbine (25%), gemcitabine (19%), capecitabine (18%), taxanes (15%), anthracyclines (10%), and other agents (10%). The remaining 4% of patients in this arm were treated with endocrine therapy. Patients in the eribulin arm achieved a significantly improved median overall survival compared with patients in the treatment of physician's choice arm (13.1 vs 10.6 months; hazard ratio, 0.81; 95% CI, 0.66-0.99; *P*=.041). The increase in median overall

survival observed in the eribulin arm compared with the treatment of physician's choice arm remained significant in an updated analysis (13.2 vs 10.5 months; hazard ratio, 0.81; 95% CI, 0.67-0.96; *P*=.014; Figure 4).[14] Although there was a trend toward improved median progression-free survival with eribulin vs the treatment of physician's choice, this difference did not reach statistical significance (3.7 vs 2.2 months; hazard ratio, 0.87; 95% CI, 0.71-1.05; *P*=.137) in the independent review assessment; in the investigator review assessment, the improvement in median progression-free survival observed was statistically significant (hazard ratio, 0.76; 95% CI, 0.64-0.90; *P*=.002). The objective response rate was significantly improved with eribulin vs treatment of physician's choice (12% vs 5%; *P*=.002).

Based on the results of the EMBRACE study, eribulin was approved for the treatment of metastatic breast cancer. However, the EMBRACE trial was limited in 2 ways: it was not powered for comparison of eribulin against the individual drugs used in the comparator arm, and it contained no quality-of-life analyses. The use of the different drugs and schedules of administration in the comparator arm precluded a reliable assessment of quality of life by complicating the timely distribution and assessment of quality-of-life questionnaires. By contrast, quality of life was included as an endpoint in Study 301, a second phase 3 trial of eribulin in which patients were less heavily pretreated and capecitabine was chosen as the comparator arm.[15] The use of this more conventional control allowed the collection of quality-of-life data. The trial enrolled 1102 women with locally advanced or metastatic breast cancer. In contrast to the EMBRACE trial, in Study 301, although there was a trend for improved survival with eribulin vs capecitabine that emerged early and persisted, it did not reach statistical significance (15.9 vs 14.5 months; hazard ratio, 0.879; 95% CI, 0.770-1.003; *P*=.056). Again, median progression-free survival was not significantly different between the eribulin and capecitabine treatment groups, when analyzed by investigator review (4.2 vs 4.1 months; hazard ratio, 0.977; 95% CI, 0.857-1.114; *P*=.736) and independent review (4.1 vs 4.2 months; hazard ratio, 1.079; 95% CI, 0.932-1.250; *P*=.305). The global health status was pooled for patients in both treatment arms. There was a clear, stepwise difference in quality of life according to treatment response. Those patients who achieved a complete response or a partial response also experienced the best global health status. Baseline, the global health status was low in both treatment groups, but it improved during treatment in both groups. Where differences in quality of life were noted between the 2 treatment arms, these appeared to reflect the differing toxicities of capecitabine and eribulin (Table 2).

Acknowledgment

Dr Twelves is a member of the Eisai Advisory Board and has received honoraria from Eisai.

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Improving Quality of Life in Patients With Metastatic Breast Cancer

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The management of patients with metastatic breast cancer involves emphasizing both duration of survival and maintenance (or improvement, if necessary) of quality of life. Quality of life in the management of patients with metastatic breast cancer encompasses several components, including maintaining or improving a patient's performance status and functional status, minimizing the side effects associated with treatment, and controlling and/or preventing the development of disease-related symptoms.

Strategies for Incorporating Quality-of-Life Goals into Patient Management

There are 2 major strategies for incorporating quality of life into the management goals for metastatic breast cancer patients. First is to ensure that the tumor-related symptoms are decreased with effective therapy (or to maintain tumor control to prevent tumor-related symptoms in patients whose disease has not yet progressed to this point). The second is to minimize the treatment-related side effects known to occur with particular therapies.

Once tumor control is achieved, clinicians tend to utilize maintenance therapies in the treatment of metastatic breast cancer. The optimal treatment regimens for maintenance therapy are those that have antitumor efficacy as well as the ability to be administered and tolerated with only low or very manageable toxicities over a long period of time. The use of maintenance treatment strategies in metastatic breast cancer is supported by data from randomized clinical trials suggesting that if patients achieve at least a partial response or prolonged stabilized disease, they are then able to experience prolonged progression-free survival and, in some cases, superior overall survival. For example, a recent prospective, randomized phase 3 multicenter trial from Korea compared maintenance therapy with paclitaxel plus gemcitabine vs observation alone in patients with metastatic breast cancer who had initially achieved disease control with 6 cycles of the same combination given as first-line treatment.[1] Patients who received maintenance treatment achieved superior survival outcomes, including median progression-free survival (7.5 vs 3.8 months; *P*=.026; Figure 5) and median overall survival (32.3 vs 23.5 months; *P*=.047; Figure 6). Although all-grade hematologic toxicities occurred more frequently in the active maintenance treatment group compared with the observation group, there was no significant difference in quality of life between the 2 arms.

Sequential endocrine therapies are of critical importance for patients with endocrine receptor–positive metastatic breast cancer. Clinicians often underutilize these regimens in patients with visceral disease. However, sequential endocrine therapy is an excellent approach to maintaining both tumor control and quality of life for many patients. The mammalian target of rapamycin (mTOR) inhibitor everolimus is one important strategy to prolong the use of sequential endocrine therapies. Stomatitis is the most frequently reported adverse event in clinical trials with everolimus and can be treatment-limiting.[2] Prophylactic use of steroid mouth rinses is a very effective way to prevent this toxicity, thereby improving the likelihood that patients will be able to continue on therapy and maximize their exposure to sequential endocrine treatment.

Trastuzumab and pertuzumab, both antibodies directed against HER2, are used in combination with taxane chemotherapy as long-term treatment in the first-line setting of metastatic breast cancer. The cytotoxic agents often chosen for combination with trastuzumab throughout multiple lines of therapy include paclitaxel, vinorelbine, or capecitabine, all of which are highly effective and have side effects that are generally manageable, enabling continued therapy. T-DM1, the trastuzumab antibody drug conjugate utilizing the vinca alkaloid emtansine, is also highly effective against HER-positive metastatic breast cancer, prolonging overall survival, and its tolerability allows for treatment that can be maintained over many months to even years.

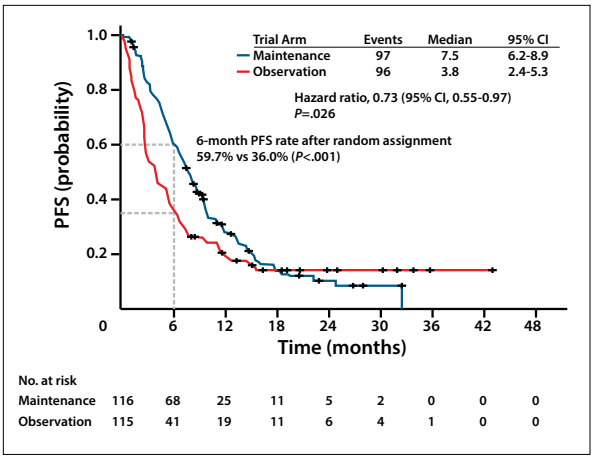

Figure 5. In a randomized phase 3 multicenter trial comparing maintenance therapy with paclitaxel plus gemcitabine vs observation alone in patients with metastatic breast cancer who had initially achieved disease control with 6 cycles of the same combination given as first-line treatment, patients who received maintenance treatment achieved superior PFS.

Adapted from Park YH et al. *J Clin Oncol.* 2013;31(14):1732-1739.[1]

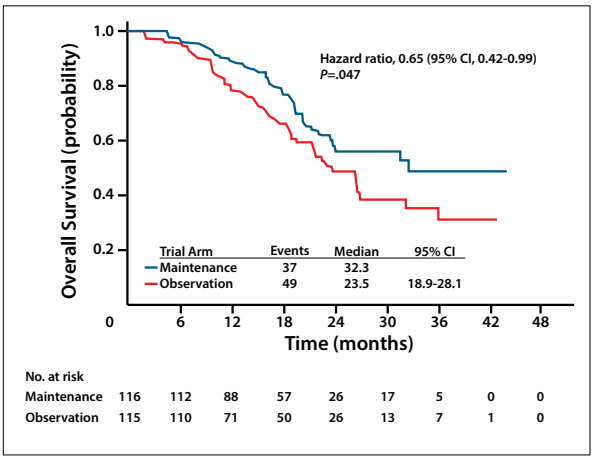

Figure 6. In a randomized phase 3 multicenter trial comparing maintenance therapy with paclitaxel plus gemcitabine vs observation alone in patients with metastatic breast cancer who had initially achieved disease control with 6 cycles of the same combination given as first-line treatment, patients who received maintenance treatment achieved superior OS.

Adapted from Park YH et al. *J Clin Oncol.* 2013;31(14):1732-1739.[1]

Another strategy to maintain quality of life in the setting of metastatic breast cancer is to avoid corticosteroid therapy, whether as an antiemetic or to prevent hypersensitivity reactions to treatment. Chronic use of corticosteroids can result in adrenal suppression, leading to fatigue and other treatment-related side effects that can negatively affect a patient's quality of life. Therefore, in patients whose metastatic breast cancer is likely to be sensitive to cytotoxic chemotherapy, it is sometimes preferable to utilize agents that do not require concomitant corticosteroid therapy, such as vinorelbine, *nab*-paclitaxel, and eribulin.

The use of bone-targeted therapies helps prevent and/or mitigate the emergence of bone pain and other skeletal-related events, such as bone fractures, that accompany the progression of metastatic breast cancer. Most patients with symptomatic visceral disease or symptomatic nonvisceral disease (ie, bony disease) require combination therapy with a cytotoxic agent in addition to an antiosteoclast agent. In general, in this setting, sequential use of single-agent cytotoxic chemotherapy has been shown to be more effective in maintaining quality of life, provided the patient's tumor burden and related symptoms do not require combination chemotherapy for more urgent control.

Combination chemotherapy regimens are generally reserved for patients with highly symptomatic metastatic disease. Some combination chemotherapy strategies, such as capecitabine combined with either a taxane or vinorelbine, are better tolerated than others. Eribulin in combination with capecitabine is also an option for patients whose disease is resistant to an anthracycline and a taxane and who have a significant tumor burden that requires combination therapy. A current very young patient of mine who presented with locally advanced triple-negative breast cancer received a preoperative combination regimen consisting of an anthracycline, cyclophosphamide, a taxane, and carboplatin. She rapidly developed a large, solitary symptomatic liver metastasis within a year of completing preoperative chemotherapy. The patient required combination chemotherapy to control her disease and reduce her symptoms, and capecitabine plus eribulin produced a near-complete clinical response and a dramatic improvement in quality of life. The use of this combination is supported by existing safety data from clinical trials (Table 3).[3] Following resection of the 1-mm area of residual disease in her liver, the patient has been able to maintain therapy with eribulin and capecitabine with excellent tolerability.

One strategy for patients receiving combination chemotherapy is to stop treatment with one of the agents after tumor control has been achieved, continuing with single-agent therapy. For example, if a patient is experiencing significant side effects with a taxane plus capecitabine, the taxane can be discontinued once cytoreduction has been accomplished, and capecitabine can continue as maintenance therapy.

The selection of cytotoxic agents for metastatic breast cancer is a critical factor influencing patients' quality of life. A treatment that can maintain excellent tumor control with manageable side effects that do not reduce the patient's quality of life can be maintained long-term to avoid the emergence of tumor-related symptoms.

Table 3. Most Common Treatment-Emergent or Serious Adverse Events in a Phase 2 Trial of Eribulin Plus Capecitabine

	Eribulin/Capecitabine (N=67)	
Treatment-Related Treatment-Emergent Adverse Events, n (%)	**All Grades**	**Grades 3/4**
Alopecia	52 (77.6)*	n/a
Fatigue	39 (58.2)	2 (3.0)
Nausea	35 (52.2)	1 (1.5)
Diarrhea	27 (40.3)	4 (6.0)
Hand-foot syndrome	27 (40.3)	12 (17.9)
Neutropenia	24 (35.8)	21 (31.3)
Constipation	23 (34.3)	n/a
Treatment-Related Serious Adverse Events		
Pulmonary embolism	3 (4.5)	3 (4.5)
Diarrhea	2 (3.0)	2 (3.0)

*Grade 1 alopecia was reported in 31 patients (46.3%).

Data from Smith JW et al. ASCO abstract 563. *J Clin Oncol.* 2013;31(15 suppl).[3]

Other strategies that have been shown to improve or maintain quality of life in patients with metastatic breast cancer include minimizing trips to the physician's office and/or the hospital, avoiding unnecessary imaging studies, and using serum tumor markers, instead of imaging, to follow disease status. Regular exercise also clearly improves patients' functional status and quality of life.

Palliative Care for Symptom Management

Palliative care is generally associated with symptom management, with a particular focus on tumor-related symptoms. Palliative care can be administered during active treatment for metastatic breast cancer, as well as when patients have decided not to pursue additional cytotoxic treatments for their disease. Palliative treatment focuses on 4 major areas: fatigue, depression, insomnia, and pain. One study reported that patients with metastatic breast cancer experienced an average of 14 symptoms, the most severe of which was pain.[4] Each of these symptoms can diminish quality of life.

It has been estimated that chronic pain occurs in 70% to 90% of cancer patients. In patients with metastatic breast cancer, chronic pain most often results from bone metastases. Interventions for chronic pain vary according to the type.[5] For neuropathic pain, adjuvant antidepressants or anticonvulsants are often used in conjunction with opioids as first-line therapy. Topical anesthetics and psychologic support may also be useful for this type of pain. Glucocorticoids are often used for inflammatory pain, whereas nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with opioids are useful for bone pain.

The most frequently reported symptom in cancer patients is fatigue, which may occur both on and off therapy. Nonpharmacologic interventions, including regular exercise and psychosocial interventions, may be beneficial in many cases. Psychostimulants can also be useful.[5] Another important point for palliative treatment of fatigue is to address underlying contributing causes, such as pain or depression.

Psychologic distress, manifest as depression and/or anxiety, is a common symptom in patients with metastatic breast cancer. Although up to one-half of patients with metastatic breast cancer are estimated to suffer from depression, actual diagnoses are rare.[6] Factors that may influence the likelihood that a patient will experience depression include fatigue, a history of depression, and feelings of helplessness or hopelessness.[5] Importantly, many of the signs associated with depression, such as fatigue, loss of appetite, and insomnia, are also attributable to the metastatic disease itself, and thus may be difficult to recognize as such. Treatment with antidepressants or anxiolytics may be beneficial, but the use of such agents should be carefully monitored because they may interfere with metabolism of some anticancer therapies.

Insomnia also affects a great proportion of patients with metastatic breast cancer. Although pharmacologic interventions may be useful as a short-term approach, it is important to consider other measures, such as cognitive behavior therapy, exercise (including yoga), and good sleep hygiene.[5]

Acknowledgment

Dr O'Shaughnessy is a consultant for Eisai, GlaxoSmithKline, Genentech, Janssen Biotech, Lilly, sanofi, and Novartis.

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General Discussion

Joyce A. O'Shaughnessy, MD I would like to emphasize the point that in order to have a major impact on quality of life, it is likely that a new agent would need to exhibit substantial antitumor activity as well as lack significant side effects. The emphasis on goals of decreasing treatment-related side effects and on effecting tumor cytoreduction will vary depending on the patient's baseline extent of tumor burden and tumor-related symptoms.

There are typically a large number of treatment choices for patients who are asymptomatic or who have minimal symptoms from their tumor. In these cases, the emphasis should be on choosing agents with lesser toxicity, which would most likely be usable as longer-term maintenance therapy. However, as the tumor burden increases and patients experience more symptoms, the goal of treatment shifts to management of tumor-related symptoms. In these cases, the best strategies are those that incorporate agents that can significantly reduce tumor volume, even in the setting of prior exposure with or resistance to therapies. For patients with metastatic breast cancer, our most valuable agents are those that are not cross-resistant and also can have a dramatic effect on tumor burden. Unfortunately, there are few such agents. Once patients become resistant to endocrine therapies or HER2-targeted agents, the cytotoxic agents with level 1 evidence to support their use in this setting include taxanes, anthracyclines, alkylators, capecitabine, and eribulin. For patients with triple-negative breast cancers, platinum-based agents may also be of benefit.

Christopher Twelves, MD One of the issues that I have become more conscious of in my own practice in the past decade is the need to discuss possible treatment options with patients. For example, capecitabine has been evaluated and used mostly as a late-line agent, but I am now more likely to discuss its use earlier in the course of therapy with a patient who is particularly adverse to experiencing alopecia or who has had problems with venous access. Certainly in the setting of symptomatic metastatic breast cancer, I am increasingly more likely to offer the patient the choice between an oral treatment—with a careful explanation of the likely side effects—and an alternative treatment, such as eribulin. In this discussion, I would emphasize that if all goes well, the patient would have the opportunity to receive both agents; the discussion centers on the sequence in which the patient would prefer to receive these therapies.

Another point involves symptomatic severity. Two decades ago, the choice of chemotherapy for palliative treatment was based primarily on the severity of the patient's symptoms. In those years, we had far fewer effective agents, and they were associated with significant toxicities, such as emesis, that could not be controlled. In comparison, the current era includes more effective therapeutic agents, better ways of controlling side effects, and improved ways of monitoring patients. I have the sense that there is now a lower symptom threshold for administering chemotherapy than there was in the past. As I treat those patients who are less symptomatic, the impact on quality of life and the potential side effects come more sharply into focus.

William J. Gradishar, MD I would concur with the need to involve the patient more in the discussion of treatment. I do not necessarily view it as a negotiation, but instead as an opportunity to make the patient more aware of the treatment options. In a setting where most of our therapies are palliative—and over the course of time, a patient will likely receive a sequence of therapies—it has become necessary to engage the patient in making the decision. If something is clearly the best therapy for a particular patient, then of course we as physicians should strongly emphasize that approach. But when there is "competition among equals" in terms of the effectiveness of therapy, we should consider which regimen would be the least toxic and permit the patient to participate in the activities that are most important to her. The patient will inevitably receive all the treatments available over time, and what is becoming clear is that the sequence of these treatments is not as critical as respecting the patient's wishes and maintaining her quality of life.

Christopher Twelves, MD Importantly, patients have different priorities. With the conventional tools used to measure quality of life, patients must address certain questions devised by investigators. Additionally, these tools do not allow patients to express how important each aspect is to them. For example, hair loss may be extremely important to one patient, whereas avoidance of a central intravenous line is more important to another. More patient-powered ways of collecting quality-of-life information and patient-reported outcome measures will perhaps better reflect the types of discussions we have with patients, in which we aim to meet their particular needs and priorities.

Acknowledgments

Dr O'Shaughnessy is a consultant for Eisai, GlaxoSmithKline, Genentech, Janssen Biotech, Lilly, sanofi, and Novartis. Dr Twelves is a member of the Eisai Advisory Board and has received honoraria from Eisai. Dr Gradishar has no real or apparent conflicts of interest to report.

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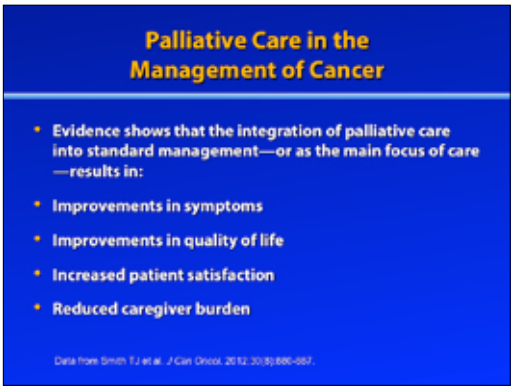

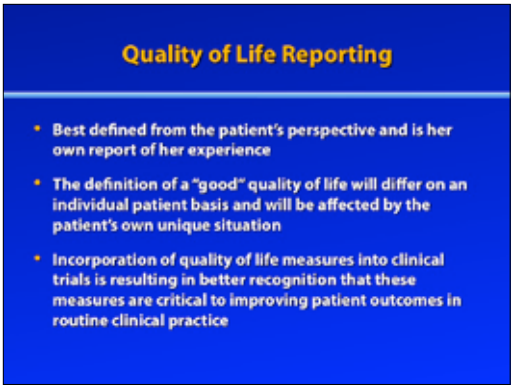

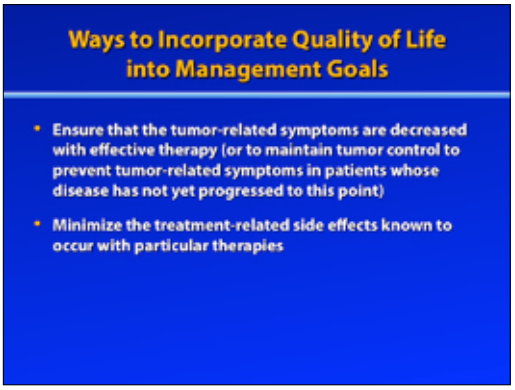

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Effective Management of Quality of Life in Metastatic Breast Cancer

CME Post-Test: *Circle the correct answer for each question below.*

1. In a trial by Project ENABLE, what type of management was associated with higher quality of life?

   a. Consolidation therapy
   b. Bone marrow transplant
   c. Palliative care
   d. Watch and wait

2. In a European survey of patients with metastatic breast cancer, what proportion of patients (or their caregivers) believed that life-extending treatment was worthwhile?

   a. 45%
   b. 54%
   c. 67%
   d. 76%

3. In a phase 3 clinical trial comparing capecitabine plus docetaxel with docetaxel alone in patients with anthracycline-treated metastatic breast cancer, which treatment was associated with a significantly higher quality of life?

   a. Capecitabine plus docetaxel
   b. Docetaxel alone
   c. There was no significant difference

4. In a phase 2 study of patients with HER2-positive metastatic or recurrent locally advanced breast cancer examining first-line treatment with either trastuzumab plus docetaxel or T-DM1, which therapy was associated with fewer grade 3 or higher adverse events?

   a. T-DM1
   b. Trastuzumab plus docetaxel
   c. There was no significant difference

5. In the phase 3 EMBRACE trial comparing eribulin with a treatment of the physician's choice, eribulin was associated with a median overall survival of:

   a. Approximately 10 months
   b. Approximately 11 months
   c. Approximately 12 months
   d. Approximately 13 months

6. In patients with metastatic breast cancer, chronic pain most often results from:

   a. Bone metastases
   b. Cardiomyopathy
   c. Edema
   d. Neuropathy

7. In a phase 3 multicenter trial comparing maintenance therapy with paclitaxel plus gemcitabine vs observation alone in patients with metastatic breast cancer, which approach was associated with superior survival outcomes?

   a. Observation alone
   b. Maintenance therapy with paclitaxel plus gemcitabine
   c. There was no significant difference

8. What is the most frequently reported adverse event in clinical trials of everolimus?

   a. Fatigue
   b. Nausea
   c. Stomatitis
   d. Pruritus

9. In a study by Portenoy and Lesage, what was the most severe symptom in patients with metastatic breast cancer?

   a. Depression
   b. Fatigue
   c. Insomnia
   d. Pain

10. Approximately how many patients with metastatic breast cancer are thought to experience depression?

    a. Up to one-third
    b. Up to one-quarter
    c. Up to one-half
    d. Up to three-quarters

Evaluation Form: Effective Management of Quality of Life in Metastatic Breast Cancer

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-Tests by Course" and search by **project ID 9670**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Hematology/Oncology ❒ Oncology, Medical ❒ Oncology, Other

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week with breast cancer?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Describe the quality of life issues faced by patients with metastatic breast cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Accurately assess quality of life in metastatic breast cancer patients
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Discuss how qualify of life impacts overall health and prognosis in patients with metastatic breast cancer
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Implement strategies to maintain or improve quality of life in metastatic breast cancer patients
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented
❒ My current practice has been reinforced by the information presented
❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

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1	2	3	4	5	6	7	8	9	10

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