Quality of Life Issues in the Treatment of Metastatic Breast Cancer

By Robert W. Carlson, MD

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The contemporary systemic treatment of metastatic breast cancer involves the sequential selection and delivery of hormonal therapies and cytotoxic chemotherapies. The available therapies for metastatic breast cancer are rarely curative,[1] although high rates of response and modest prolongation of survival may be achieved in association with varying degrees of treatment-related toxicity. Therefore, selection of appropriate therapy requires a reasoned consideration of the likelihood of benefit from therapy balanced with the impact of the therapy on the patient’s quality of life. Unfortunately, relatively little objective evidence is available regarding the impact of most systemic therapies on the quality of life of patients with metastatic breast cancer.

Quality of Life Measurement

The quality of life in patients with cancer has many dimensions (Table 1). A number of reliable and valid instruments have been developed to measure quality of life in patients with cancer, and some have been specifically developed to assess quality of life in patients with breast cancer.[2-7] None of the available instruments has been universally accepted. These instruments include:

- Time Without Symptoms and Toxicity (TWiST)
- Quality of Time Without Symptoms and Toxicity (Q-TWist)
- Quality-Adjusted Life Year (QALY), Quality of Well Being (QWB)
- Cancer Rehabilitation Evaluation System (CARES)
- European Organization for Research and Treatment of Cancer QLQ-C30
- Functional Assessment of Cancer Therapy (FACT)
- Functional Living Index—Cancer (FLIC)
- Selby Linear analogue Self-assessment (LASA) scale
- Rotterdam Symptom Check List (RSCL).

All of these instruments require time and resources to administer and expertise to analyze. As a result, the use of the quality of life instruments has been limited primarily to research studies involving women with local-regional breast cancer. Even in the research setting, few randomized clinical trials have incorporated quality of life assessments other than the use of measurements of physical performance by the Karnofsky or Eastern Cooperative Oncology Group (ECOG [Zubrod, World Health Organization]) scales.[8,9] Instruments that efficiently and comprehensibly measure quality-of-life will be required before routine quality of life measurements will be used in the nonresearch setting.

In the absence of formal quality-of-life assessments in clinical trials, the clinician must balance...
antitumor activity, performance status, and the usual toxicity measures (eg, nausea, myelosuppression, asthenia) as surrogates for quality of life associated with each specific systemic therapy.

**Hormonal Therapy**

The hormonal therapies have the quality-of-life advantages of limited and usually non-threatening acute toxicity, rare chronic toxicity, need for infrequent visits to health care providers, oral administration, and, in appropriately selected patients, response and duration of response rates equivalent to the cytotoxic agents. Tamoxifen (Nolvadex) remains the most commonly used first-line hormonal agent and has a favorable and acceptable toxicity profile. New estrogen antagonists (toremifene [Fareston], droloxifene) appear to have therapeutic indices similar to those of tamoxifen, although further study is needed before firm conclusions may be made.[10,11] The recent addition of new aromatase inhibitors (anastrozole [Arimidex], letrozole [Femara]) for the treatment of postmenopausal women provides increased ease of administration, decreased acute and chronic toxicity, and excellent rates of response in comparison with aminogluthethimide (Cytadren) and many of the other second- and third-line hormonal agents.[12-14]

**Cytotoxic Therapy**

A number of cytotoxic agents have activity in the treatment of metastatic breast cancer. The active single agents differ substantially in their toxicity profiles, although the dose-limiting toxicity is usually myelosuppression. Combination chemotherapy regimens are usually used for first-line cytotoxic treatment of metastatic breast cancer. When cytotoxic agents are used in combination regimens, the toxicity experienced is a combination of that observed with the single agents. Because of their additive nature, the most frequently used combinations (eg, CMF [cyclophosphamide/methotrexate/5-fluorouracil], CAF [cyclophosphamide/Adriamycin/5-fluorouracil]/FAC, CEF [cyclophosphamide/epirubicin/5-fluorouracil]) have similar rates of response and toxicities.

Response Predicts Quality of Life

An early study addressed the quality of life of women with metastatic breast cancer using a linear analogue self-assessment scale.[15] This study compared the quality of life of women with metastatic breast cancer randomized to receive hormonal therapy versus combination chemotherapy with cyclophosphamide (Cytoxan, Neosar), doxorubicin (Adriamycin), 5-fluorouracil (5-FU) and vincristine (Oncovin). A total of 25 parameters of quality of life were measured, and, as expected, patients receiving cytotoxic therapy experienced more alopecia, nausea, vomiting, and constipation than those treated with hormonal maneuvers. However, there was a trend toward improved well-being in patients receiving cytotoxic therapy that became statistically significant by week 11 of therapy. This study was initiated prior to the availability of reliable hormone receptor determinations that would have selected a cohort of women who are likely to respond to hormonal therapy (Table 2). Thus, the objective response rate was higher in the cytotoxic therapy group. The improved well-being with cytotoxic therapy was related to the achievement of an objective response. Thus, achievement of an objective response appears to be a strong predictor of quality of life despite the acute toxicity of cytotoxic therapy.

A trial in women with metastatic breast cancer compared treatment with continuous versus intermittent CMF plus prednisone or doxorubicin plus cyclophosphamide chemotherapy.[16] Patients in the continuous arm received chemotherapy until progression of disease, while those in the intermittent arm received three cycles of chemotherapy and then received additional chemotherapy only at the time of progression. Continuous chemotherapy was associated with higher rates of response and superior time to progression. There was a trend toward superior survival with continuous treatment. Surprisingly, both patient and physician assessments of patient quality of life were superior for those patients receiving continuous therapy. This confirms findings from the earlier study of Baum et al[15] that response is associated with improved quality of life. Another trial incorporating a quality-of-life assessment compared two dose levels of CMF in patients with metastatic breast cancer.[17] Higher dose CMF compared with lower dose CMF was associated with improved rates of response, improved median survival, and more vomiting, myelosuppression, conjunctivitis, and alopecia. The quality of life assessment demonstrated similar scores for both the higher and lower dose CMF regimens, although most scores favored the higher dose regimen. Thus, the higher dose CMF regimen appeared to produce superior palliation compared with the lower dose CMF regimen.
New Cytotoxic Agents

Recently, several new cytotoxic agents with substantial activity against breast cancer have become available. These agents include the taxanes (paclitaxel [Taxol] and docetaxel [Taxotere]) and vinorelbine (Navelbine).

Paclitaxel

In single-agent phase II trials in women with metastatic breast cancer, paclitaxel appears to result in response rates of 23% to 56% \(^\text{[18-25]}\). Randomized trials comparing single-agent paclitaxel with single-agent doxorubicin show either inferior\(^\text{[26]}\) or equivalent\(^\text{[27]}\) rates of response with paclitaxel. The common nonhematologic toxicities of paclitaxel include peripheral sensory neuropathy that is only partially reversible, myalgias and arthralgias, and, with some doses and schedules, allergic reactions in the non-premedicated patient. The combination of paclitaxel and doxorubicin has superior rates of response, increased toxicity, no apparent survival benefit, and equivalent negative impact on quality of life when compared with single-agent doxorubicin or single-agent paclitaxel.\(^\text{[27,28]}\) Several other paclitaxel-containing combinations are the focus of ongoing clinical trials.

Docetaxel

Single-agent docetaxel results in rates of response of 32% to 68% in patients with metastatic carcinoma of the breast \(^\text{[29-33]}\). A randomized trial comparing docetaxel with single-agent doxorubicin demonstrated a 47% rate of objective response with docetaxel compared with 32% with doxorubicin.\(^\text{[32]}\) Early studies of combination docetaxel plus doxorubicin demonstrated very high rates of response, but confirmation of these results in randomized trials has not yet been performed.\(^\text{[34]}\) Phase III studies of single-agent docetaxel versus paclitaxel are ongoing and should provide important information about comparative antitumor efficacy. Docetaxel-based combination chemotherapy regimens are also under active investigation. Docetaxel is associated with the nonmyelosuppressive toxicities of edema with or without serosal effusions, hypersensitivity reactions, skin and nail changes, and occasional peripheral sensory neuropathy. The use of dexamethasone for 3 to 5 days with treatment substantially decreases the frequency and severity of the associated edema and effusions.

Vinorelbine

Vinorelbine has demonstrated single-agent rates of response of 32% to 52% in patients with metastatic breast cancer \(^\text{[35-42]}\). A randomized comparison of vinorelbine versus melphalan in anthracycline-refractory breast cancer demonstrated superior rates of objective response, time to progression, and survival with vinorelbine.\(^\text{[43]}\) A formal quality-of-life assessment was performed in this study.\(^\text{[43,44]}\) No significant differences between the quality of life of vinorelbine- versus melphalan-treated patients were observed. This study has been criticized because of the use of melphalan in the control arm, an agent with limited activity in the treatment of breast cancer. However, melphalan is also an agent with minimal toxicity, suggesting that vinorelbine is an agent with a very acceptable toxicity profile. A number of phase II trials of vinorelbine in combination with other agents have been performed with encouraging rates of response.\(^\text{[45]}\) Additional phase III trials in metastatic breast cancer of vinorelbine as a component in combination regimens are ongoing.

An oral formulation of vinorelbine is available for research purposes and may provide the advantage of not requiring intravenous access, requiring fewer visits to the health care professional, and providing the patient with a greater sense of control of their treatment. Early studies do suggest an increased rate of gastrointestinal toxicities, but these toxicities appear to be manageable with prophylactic antiemetic and antidiarrheal agents.\(^\text{[46,47]}\)

Gemcitabine

Gemcitabine (Gemzar), another new agent, appears to have activity in some early clinical trials, with response rates of 0% to 46% \(^\text{[3]}\). Nonhematologic toxicity appears to be mild and consists mainly of a flu-like syndrome.

Combination Regimens Using New Cytotoxic Agents

The toxicity profiles of the new single agents allow their exploitation as components in combination chemotherapy regimens. These combination chemotherapies use multiple active cytotoxic agents and generally have high rates of response but with increased severity of hematologic and nonhematologic toxicities. Whether these regimens will be associated with superior durations of response and survival and improved quality of life awaits the completion of randomized clinical trials. There is a need for the further development and use of valid, reliable, easily administered and scored measures of quality of life. Only with the availability of studies incorporating quality-of-life
measures across multiple dimensions will patients and physicians be able to balance treatment activity with quality-of-life considerations.

**Discussion**

**Dr. Weeks:** You talked about the possible role of vinorelbine as an oral agent for women with metastatic breast cancer. Are oral combination regimens a viable option in this setting?

**Dr. Carlson:** Yes. Oral combination regimens offer an excellent approach for patients with metastatic breast cancer. One difficulty, however, is that relatively few of the agents active against metastatic breast cancer can be administered orally. The vinca alkaloids and the anthracyclines, for example, cannot be given orally, at least not yet. Certainly the alkylating agents can be given as part of combination treatment. I am not aware of any randomized trials assessing oral combination regimens for patients with metastatic breast cancer.

**References:**


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