Therapeutic Options in the Management of Metastatic Breast Cancer

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Novel agents are adding to the wide choices of standard chemotherapies already available. This review offers an approach to the selection of individualized and rational therapies for patients with metastatic breast cancer.

ABSTRACT: Breast cancer is the second leading cause of cancer-related death in women in the United States, and for nearly all with metastatic disease at presentation or relapse it will be incurable. The goals of therapy are to optimize quality of life and, if possible, prolong time to progression of disease and death. For a select group of patients an aggressive surgical approach may be considered. Initial palliation with endocrine therapy should be the primary consideration for patients with metastatic hormone receptor-positive tumors. Cytotoxic chemotherapy is appropriate for those with hormone-refractory disease, rapidly progressive visceral disease, or early relapse after adjuvant therapy. If a tumor overexpresses HER2, targeted treatment with trastuzumab (Herceptin) or lapatinib (Tykerb) is possible. Consequently, accurate determination of the status of these predictive markers in tissue (possibly from a recurrence site) is key. Other novel agents are adding to the wide choices of standard chemotherapies already available. This review offers an approach to the selection of individualized and rational therapies for patients with metastatic breast cancer.

Breast cancer is the second leading cause of cancer-related death in women in the United States,[1] and for nearly all with metastatic disease at presentation or relapse it will be incurable. The goals of therapy are to optimize quality of life and, if possible, prolong time to progression of disease and death. A larger armamentarium of therapeutic options is available to physicians in 2008 than ever before. This wide choice brings its own challenges.

Wherever possible, tissue samples should be obtained for histologic confirmation of metastatic disease, particularly in the case of isolated lung or liver lesions where competing cancers may present and for a current assessment of hormonal receptor and HER2 status. Management of these patients is best conducted within a multidisciplinary team including palliative medicine, surgical, and radiation oncology. Here, we will focus on available systemic treatments for the patient with metastatic breast cancer.

Diagnostic Evaluation of Patients With Presumptive Diagnosis of Metastatic Disease

FIGURE 2
Metastatic breast cancer may be an incidental finding in asymptomatic patients or may present with nonspecific symptoms of malaise or weight loss. The earlier detection of asymptomatic lesions on imaging studies prompted by elevated circulating markers (neither recommended for routine surveillance in an asymptomatic patient after adjuvant therapy), with or without the earlier initiation of treatment, will not necessarily increase overall survival and may only result in lead-time bias. Wherever possible, tissue samples should be obtained for histologic confirmation of metastatic disease, particularly in the case of isolated lung or liver lesions, where competing cancers may present, and for current assessment of hormonal-receptor and HER2 status to assist with therapy selection. These can also be used as modest prognostic factors along with time to recurrence, extent of the disease, location, prior therapy, symptoms related to the disease, and performance status. Solitary lesions on isotope bone scans or computed tomography should be interpreted with caution. Imaging studies without tissue confirmation may be acceptable in the appropriate setting, such as when multiple areas of osseous metastases or multiple sites with visceral involvement are present. Adequate baseline staging also serves to allow evaluation of response to planned therapy. Fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is being used increasingly in the detection of occult recurrent breast cancer, but remains inferior to bone scans for the assessment of blastic lesions and should not be used without concomitant computed tomography (CT) for fusion images. An FDG-PET/CT study is costlier than a CT scan with oral/IV contrast and a bone scan, and data showing improved decision-making and outcomes are lacking at present. Evidence is insufficient to support using tumor markers like CA 27-29 or carcinoembryonic antigen (CEA) on their own to monitor response to therapy, although these assessments may help determine tumor progression in patients with metastatic (but no measurable) disease.

**Multimodality Therapy With Curative Intent for Those With Oligometastatic Disease**

For a select group of patients, an aggressive surgical approach may be considered. One retrospective review found an increased survival in women with limited advanced disease who underwent resection of the primary tumor in addition to systemic therapy, but these studies are frequently affected by selection bias. A single prospective study reported a 24% 15-year disease-free survival among women who were treated with systemic anthracycline-based therapy following locoregional salvage therapy (surgical resection with or without radiation) of a solitary metastasis. A planned prospective trial to be led by the Eastern Cooperative Oncology Group (ECOG) will randomize newly diagnosed metastatic breast cancer patients with intact primary tumors and disease responsive to initial systemic therapy to have surgical resection and radiotherapy vs no local therapy.

**Therapy for Hormone Receptor-Positive Disease**

TABLE 1
Commonly Used Endocrine Regimens for Metastatic Breast Cancer

<table>
<thead>
<tr>
<th>Initial Endocrine Therapy Options</th>
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<tr>
<td>Premenopausal patients: tamoxifen or ovarian function suppression</td>
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<tr>
<td>Postmenopausal patients: aromatase inhibitor or tamoxifen*</td>
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<th>Subsequent Endocrine Therapy Options</th>
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<tr>
<td>Premenopausal patients: ovarian function suppression with tamoxifen or an aromatase inhibitor*</td>
</tr>
<tr>
<td>Postmenopausal patients: nonsteroidal (anastrozole, letrozole) or steroidal ( exemestane) aromatase inhibitor*</td>
</tr>
<tr>
<td>Fulvestrant</td>
</tr>
<tr>
<td>Tamoxifen or toremifene</td>
</tr>
<tr>
<td>Megestrol acetate</td>
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<tr>
<td>Fluoxymesterone</td>
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<td>Ethinyl estradiol</td>
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In view of its highly preferable toxicity profile, initial palliation with endocrine therapy should be the primary consideration for patients with metastatic hormone-receptor-positive tumors. Only in the rare setting of imminent vital organ failure or symptomatic visceral disease should a rapid response from cytotoxic chemotherapy be sought over a trial of endocrine therapy (Table 1). There is no justification for combining antiestrogens with chemotherapy, and data from the adjuvant setting suggest inferior outcome with this strategy.[8]

Daily tamoxifen is the most commonly used selective estrogen-receptor modulator (SERM). Third-generation aromatase inhibitors including anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin) are associated with improved progression-free and overall survival compared to tamoxifen in postmenopausal women.[9] Direct comparison as second-line therapy in metastatic breast cancer shows no convincing clinical advantage of one aromatase inhibitor over another.[10] There is little evidence regarding the optimal sequence of therapy (ie, a SERM followed by an aromatase inhibitor or vice versa), and most patients will be treated with both during the course of their disease.

Prior exposure to specific antiestrogens in the adjuvant setting may influence choice of antiestrogen therapy in the metastatic setting. The selective estrogen-receptor downregulator fulvestrant (Faslodex) is active in postmenopausal women with tamoxifen-resistant disease, is as effective as aromatase inhibitors in the second-line setting, and can also be used after progression on an aromatase inhibitor.[11,12]

The combination of tamoxifen and a luteinizing hormone-releasing hormone (LHRH) agonist is associated with increased overall and progression-free survival in premenopausal women with metastatic disease and functional ovaries.[13] Combination therapy is associated with an increased incidence of menopausal symptoms, and it is not unreasonable to use tamoxifen alone in women with low-volume disease. Few data are available regarding the use of LHRH agonists with an aromatase inhibitor.

Women whose tumors do not express hormone receptors and those who have shown progression following hormonal interventions are considered hormone-insensitive and should be recommended for chemotherapy-based therapies if possible.

When to Initiate Systemic Chemotherapy and Choosing a Chemotherapy Drug

Breast cancer is a relatively chemosensitive disease. As discussed above, endocrine manipulation should be considered for all patients with hormone-receptor-positive disease and small volume, bone-only or asymptomatic visceral disease. Cytotoxic chemotherapy is appropriate for those with
hormone-refractory disease, rapidly progressive visceral disease, or early relapse after adjuvant therapy. It is the only therapeutic option for patients with HER2-negative, hormone-resistant metastatic breast cancer. TABLE 2

<table>
<thead>
<tr>
<th>Commonly Used Chemotherapy Regimens for Metastatic Breast Cancer</th>
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| Given the wide choice of available agents, it is paramount to individualize therapy as much as possible. Pertinent physician and patient factors in treatment choice include performance status, personal preference or experience, compliance, drug administration route, comorbidities, drug toxicities, efficacy, and prior exposure to the same drug class (Table 2). Circulating tumor cells can be detected in a small percentage of patients with metastatic disease and are an early predictor of progression.[14,15] However, their clinical utility in directing a change in therapy and their impact on clinical outcome has not yet been determined and is the subject of a prospective randomized trial.

**Sequential Single Agents vs Combination Chemotherapy**

A Cochrane review in 2005 found that, compared with single chemotherapeutic agents, combination regimens showed a statistically significant advantage for tumor response and time to progression in women with metastatic breast cancer, a modest improvement in overall survival, and significantly worse toxicities.[16] Administering agents sequentially has the advantage of giving each drug at its maximum tolerated dose without overlapping toxic effects. The emergence of newer targeted agents that do not or only modestly exacerbate the adverse effects of most conventional cytotoxic agents allow for safe combinations and, in some cases, improved survival (eg, trastuzumab [Herceptin]). At present, combination chemotherapy in the metastatic setting is best reserved for select, fit patients with rapidly progressing disease. Improved prognostic and predictive tools will hopefully help with drug selection in the future.

**Anthracyclines**

Since the 1970s, doxorubicin has shown increased response rates over non-anthracycline-containing regimens.[17,18] No significant difference in efficacy was noted between epirubicin (Ellence) and doxorubicin in the metastatic setting in a trial comparing CAF (cyclophosphamide, doxorubicin, fluorouracil [5-FU]) with CEF (cyclophosphamide, epirubicin, 5-FU).[19] Pegylated liposomal doxorubicin (Doxil) has shown comparable antitumor activity and less cardiotoxicity than conventional doxorubicin.[20] Doxorubicin-containing regimens are available in multiple dosing and scheduling formats.

Following the results demonstrated by the Early Breast Cancer Trialists’ Collaborative Group that anthracycline-based adjuvant polychemotherapy reduces the annual breast cancer death rate by about 38% for women younger than 50 years and by about 20% for those aged 50 to 69 years,[21] many women with recurrent disease will already have received anthracycline-based chemotherapy regimens and often taxanes. The same is true for many endocrine manipulations, and it is unclear whether rechallenge with anthracycline-containing regimens is effective as a first-line therapy. One small retrospective study was designed to address this issue.[22] This randomized phase III trial compared the efficacy of epirubicin plus docetaxel (Taxotere) with that of docetaxel alone as first-line chemotherapy of metastatic breast cancer patients pretreated with epirubicin in the adjuvant or neoadjuvant setting. Antitumor efficacy was similar in the two arms, while epirubicin/docetaxel produced significantly worse leukopenia, nausea, and stomatitis. These data suggest that rechallenge with an anthracycline-containing regimen as first-line therapy in anthracycline-pretreated metastatic breast cancer patients may not be worthwhile.

**Taxanes**
Given many patients’ prior exposure to anthracyclines and their associated cardiotoxicity, taxanes are an appealing first-line metastatic chemotherapy choice. Both docetaxel and paclitaxel have been compared with doxorubicin in the first-line treatment of metastatic breast cancer. Docetaxel produced a higher overall response rate than doxorubicin (47.8% vs 33.3%; P = .008) but no difference in time to progression or overall survival.[23] A more recent study compared every-3-week single-agent docetaxel to paclitaxel and found superior overall survival and time to progression in the docetaxel arm given at a dose of 100 mg/m2; however, this treatment was associated with an increase in hematologic and nonhematologic toxicities.[24] Weekly paclitaxel is superior to the same drug given every 21 days.[25] Weekly paclitaxel and 3-weekly docetaxel have yet to be directly compared, but they appear to be equally efficacious in the adjuvant setting.[26] Anecdotal reports suggest that weekly paclitaxel after its adjuvant use in a 3-weekly or dose-dense schedule may be effective. Albumin-bound paclitaxel (nab-paclitaxel [Abraxane]) every 3 weeks produces a higher response rate (33% vs 19%; P = .001) and time to progression (23 vs 16.9 weeks; P = .006) in metastatic breast cancer patients, with potentially less associated toxicity.[27] Weekly nab-paclitaxel has not been compared to weekly paclitaxel. A randomized phase II study found greater progression-free survival with nab-paclitaxel (at all of three different doses) compared to docetaxel.[28] Avoidance of steroid premedication is a key feature of nab-paclitaxel, but cost compared to generic paclitaxel should be considered in the absence of efficacy data. Taxanes have been combined with various other chemotherapies. A meta-analysis of 12 of these studies found increased response rates and progression-free survival for the taxane/anthracycline combinations over single-agent taxanes, but this did not translate to an overall survival advantage.[29]

Other Chemotherapy Agents

Capecitabine (Xeloda) has a high single-agent efficacy in metastatic breast cancer,[30] although it is potentially less active in patients with hormone receptor-negative disease.[31] For women transitioning from oral endocrine treatments or those who wish to avoid infusion therapy and alopecia, the drug is an attractive option. However, it requires a compliant patient and can cause neutropenia, nausea, fatigue, diarrhea, and hand-foot syndrome. Use of capecitabine upfront as palliative therapy may also limit the subsequent use of bevacizumab (Avastin), an additional consideration in light of the 2008 US Food and Drug Administration (FDA) approval of this antibody for use with paclitaxel in the first-line setting. Capecitabine has been combined with docetaxel with increased response rates and increased toxicity.[32] See below for discussion of capecitabine combined with trastuzumab.

Gemcitabine (Gemzar) can be used in combination with paclitaxel for women who have previously received anthracyclines[33] and has considerable antitumor activity as a single agent[34] or in combination with paclitaxel.[35] Intravenous vinorelbine has shown responses in metastatic breast cancer after anthracycline and taxane failure.[36,37] Other available and useful treatments for multiply treated and relapsed patients include the platinum compounds and 5-FU.

Ixabepilone (Ixempra) is a member of a new class of antitubulin agents that lacks cross-resistance with the taxanes. As a single agent in the metastatic setting, it showed promise in phase II trials[38,39] and has recently been combined with capecitabine, showing increased objective response rates over capecitabine alone (35% vs 14%) in anthracycline- and taxane-resistant metastatic or locally advanced breast cancer.[40] Grade 3/4 treatment-related sensory neuropathy (21% vs 0%), fatigue (9% vs 3%), and neutropenia (68% vs 11%) occurred more frequently with combination therapy, as did death as a result of toxicity (3% vs 1%, with patients who had liver dysfunction [≥ grade 2 liver function tests] at greater risk). Therefore, this drug should be used with caution especially, when combined with other agents.

Bevacizumab

Bevacizumab is a recombinant, humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). In a recent trial, patients with untreated metastatic breast cancer and HER2-negative disease were randomly assigned to receive either paclitaxel and bevacizumab or paclitaxel alone. The combination significantly prolonged progression-free survival compared with paclitaxel alone (median, 11.8 vs 5.9 months; hazard ratio for progression = 0.60; P < .001) and increased the objective response rate (36.9% vs 21.2%, P < .001). The overall survival rate, however, was the same in the two groups (median = 26.7 vs 25.2 months). Hypertension,
proteinuria, headache, and cerebrovascular ischemia and infection were more frequent in patients receiving paclitaxel plus bevacizumab.[41]

A study of first-line bevacizumab in combination with capecitabine in HER2-negative breast cancer demonstrated an overall response rate of 38.5%[31] but a disappointingly low rate of response in patients with estrogen receptor–negative disease. Other groups are looking at combinations of bevacizumab with nab-paclitaxel and docetaxel, but to date these studies are small and prospective data are lacking. Currently, there are no data to support the continuation of bevacizumab with another chemotherapy agent upon disease progression. A randomized adjuvant trial is ongoing in North America.

Therapy for HER2-Positive Disease

If a tumor overexpresses HER2 (either by immunohistochemistry or by fluorescence in situ hybridization), targeted treatment is possible with the monoclonal antibody trastuzumab or the newer tyrosine kinase inhibitor (TKI) lapatinib (Tykerb). As a single agent given weekly, trastuzumab was established as safe and effective in patients whose tumors had already progressed through prior chemotherapies[42] or as a first-line therapy.[43,44] It was subsequently shown to have substantial activity when combined with an anthracycline/cyclophosphamide regimen or single-agent paclitaxel,[45] but excessive cardiac toxicity limits the ability to combine trastuzumab with anthracyclines.

Docetaxel or vinorelbine in combination with trastuzumab have shown comparable efficacy and tolerability to trastuzumab and paclitaxel.[46,47] Recent data show response rates of up to 48% in patients previously treated with trastuzumab who were treated with a combination of capecitabine and trastuzumab.[48] Data on continuation of trastuzumab with a new chemotherapy drug upon progression are lacking.

Certainly the importance of trastuzumab in the treatment of HER2-overexpressing metastatic breast cancer is great. However, the optimal sequence in which to give the agent has yet to be tested—ie, trastuzumab followed by the addition of chemotherapy or the combination upfront. The Trastuzumab in Dual HER2 ER-positive Metastatic breast cancer (TAnDEM) trial showed for the first time a doubling of progression-free survival and a statistically significant (though clinically less meaningful) improvement in time to progression and overall response rate when trastuzumab was added to anastrozole.[49] However, the time to progression in both arms was disappointingly low, suggesting that patients with HER2-positive disease are less likely to benefit from endocrine therapy in general.

Lapatinib is a small-molecule dual tyrosine kinase (epidermal growth factor receptor [EGFR] and HER2) inhibitor recently approved for use in combination with capecitabine for the treatment of patients who have progressive disease on trastuzumab. In a heavily pretreated population, it produced a longer median time to progression than those treated with capecitabine alone.[50] Unlike the monoclonal antibody trastuzumab, the small molecule lapatinib crosses the blood-brain barrier, and a lower incidence of central nervous system progression was observed in an updated report of the lapatinib/capecitabine arm of this trial.[51] This regimen also has central nervous system activity after progression on lapatinib.[52] Moreover, lapatinib is associated with a superior time to tumor progression when combined with paclitaxel vs paclitaxel alone, but offered no benefit in patients with HER2-negative disease.[53]

Pertuzumab and trastuzumab bind to distinct epitopes of the HER2 extracellular domain, and pertuzumab appears to perturb the ability of HER2 to homo- or heterodimerize. The addition of pertuzumab to trastuzumab after disease progression on trastuzumab alone appears active and well tolerated.[54] Trials with pertuzumab monotherapy are ongoing. The immunoconjugate combination of trastuzumab with a highly potent antimicrotubule drug derived from maytansine (T-DM1) is also active in this setting.[55]

Triple-Negative Disease

Options for patients with estrogen receptor/progesterone receptor/HER2–negative (triple-negative) metastatic breast cancer are limited. These “basal-like” tumors are seen more commonly in BRCA1-mutation carriers and appear sensitive to platinum-based therapies. Recent preliminary data from the Translational Breast Cancer Research Consortium (TBCRC) trial 001 showed no meaningful activity when using the anti-EGFR monoclonal antibody cetuximab (Erbitux) as a single agent in
triple-negative disease, and data on the combination with carboplatin will be presented at the 2008 annual meeting of the American Society of Clinical Oncology (ASCO).[56]

Others found response rates of 49% among the subset of triple-negative tumors treated with weekly irinotecan (Camptosar), carboplatin, and cetuximab in a phase II trial,[57] but this regimen was associated with higher rates of thrombocytopenia, diarrhea, and grade 3/4 neutropenia. Inhibitors of peroxisome proliferator-activated receptor gamma are now being tested in this setting.

**Novel Agents**

The use of multitargeted TKIs of VEGF in metastatic breast cancer is an area of ongoing growth. Agents including axitinib, sunitinib (Sutent), sorafenib (Nexavar), and pazopanib are being examined in this setting. TKIs of EGFR such as erlotinib (Tarceva) and gefitinib (Iressa) have negligible activity as single agents in metastatic breast cancer and are being tested in combination with other targeted drugs. Sunitinib has activity as a single agent in heavily pretreated patients with metastatic breast cancer[58] and is now being tested in combination regimens with taxanes and other drugs.

**Enrolling Metastatic Breast Cancer Patients in Investigational Studies as First-Line Therapy**

The topic of enrolling metastatic breast cancer patients in clinical trials before using standard chemotherapy is an emotive one. However, academic endeavours must be encouraged if progress is to continue and new agents developed.

A prospective, randomized phase III trial to evaluate the safety and efficacy of using a phase II agent before initiating therapy with standard combination chemotherapy in metastatic breast cancer patients was performed by the Cancer and Leukemia Group B during the 1990s.[59] Women with measurable metastatic breast cancer, previously untreated with chemotherapy for their metastatic disease, were randomized to receive either immediate chemotherapy with CAF, which was standard of care at that time, or up to four cycles of one of five sequential regimens of single-agent drugs followed by CAF.

The toxicity of each single agent followed by CAF was comparable to that of CAF alone. The cumulative response rates and overall survival for the single agent followed by CAF were not statistically different from those of CAF alone, but in the multivariate analysis, patients with visceral disease had a trend toward lower response rates on the arm where a phase II agent was followed by CAF at progression.[59] Therefore, upfront use of investigational agents in patients with metastatic breast cancer followed by standard chemotherapy options at the time of progression is a valid and safe option to be discussed with patients.

**Transitioning to Palliative Care**

A good performance status and wide choice of therapeutic agents, even in the face of progressive disease, will allow most patients with breast cancer to pursue several lines of treatment. In the absence of progressive symptoms or overt disease progression, patients should be restaged radiologically after 3 or 4 months of therapy to assess response. Patients with a more indolent process are restaged less frequently.

The decision to stop active disease-directed treatments is rarely simple. Quality of life, adverse effects of treatment, performance status, and end-of-life wishes must be considered and discussed with patients, their caregivers, and their health-care providers. The early introduction of palliative care while patients are still on active chemotherapy may help the transition to palliative care alone in later disease stages.

**Supportive Care**

Systemic anticancer therapies are only one part of the multilayered management of patients with metastatic breast cancer. These patients should have a wide range of multidisciplinary support including representatives of other medical specialties as well as nutrition, psychology, nursing, and palliative services.

Bone is the most common site of breast cancer recurrence. Bisphosphonates have been shown to reduce the incidence of skeletal-related events and may be a useful adjunct to conventional measures for control of bone pain.[60] An effect on skeletal morbidity outcomes is not seen before 6 months of therapy, and a reduction in the need for orthopedic surgery becomes significant only after
12 months. It is reasonable, therefore, to offer bisphosphonates to all breast cancer patients with bone metastases, with the exception of patients who have an expected survival of less than 6 months and well-controlled bone pain.

No evidence from clinical trials addresses the optimal duration of bisphosphonate therapy. Safety data beyond 2 years is sparse, and complications such as osteonecrosis of the jaw are increasingly being reported after longer durations of treatment with more potent IV bisphosphonates. ASCO guidelines suggest that treatment be continued until evidence of a substantial decline in the patient's performance status appears.

The use of erythropoiesis-stimulating agents (ESAs) for chemotherapy-induced anemia is an area of ongoing study. While these agents can be considered in patients with chemotherapy-induced anemia, data are not sufficient to exclude the possibility of shortened survival and tumor progression in various tumor settings including breast cancer. Potential restrictions on the use of ESAs were being considered by the FDA in early 2008.

**Conclusions**

The treatment of metastatic breast cancer remains challenging. New biologic and targeted agents are adding to the wide choices of standard chemotherapies already available. Increasingly, these new drugs will be considered for testing in patients with early-stage disease once safety data become available in metastatic breast cancer studies. Duration of therapy for the new, more expensive biologic drugs is becoming a critical issue for individuals and society, as recently exemplified by the monoclonal antibody bevacizumab.

It is also becoming increasingly clear that metastatic breast cancer is a heterogeneous disease, and there is no single optimal strategy for all patients. Many patients have an indolent course of progression, and those with limited stage IV disease are being considered for surgery and multimodality therapy with the goal of further improving their survival. Ultimately, physicians should be guided to rational and flexible treatment regimens for their patients by current best clinical guidelines and ongoing research.

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