Update on the Management of Advanced Breast Cancer

Review Article [1] | May 01, 1999
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Drs. Fornier, Munster, and Seidman provide a comprehensive update of the management of metastatic breast cancer. They review the latest innovations in both chemotherapy and hormonal therapy for advanced disease, and demonstrate just how much the treatment of breast cancer has evolved over the past decade. In addition, the authors detail results from the recent trials of trastuzumab (Herceptin).

Clinicians and patients now have more choices than ever before, and the list of active agents continues to expand. Many available therapies for metastatic breast cancer can provide excellent palliation of symptoms. Many physicians have long been convinced that the treatment of metastatic breast cancer also prolongs survival, but there is now preliminary evidence that patients may be living longer as a result of new treatments that are available. The challenge faced by clinicians is how and when to use all of the new therapies to maximize patients’ survival and quality of life.

Advantages of Single-Agent Therapy

In recent years, there has been a growing tendency for physicians to use sequential single agents in the treatment of metastatic breast cancer. Fornier et al highlight three trials in which combinations were compared with single agents. In each of these studies, patients receiving single agents appeared to do at least as well as those treated with combination therapy.

The most important of these trials, conducted by Sledge et al from the Eastern Cooperative Oncology Group (ECOG), was a three-arm, randomized trial comparing doxorubicin, paclitaxel (Taxol), and a combination of the two agents. Patients given single-agent therapy crossed over to the other agent at the time of disease progression. Although combination therapy resulted in a higher response rate and longer time to progression than either of the single agents, the sequential use of single agents resulted in equivalent survival and quality of life. Monotherapy has many potential advantages. Most importantly, the use of single agents avoids exposing patients to treatments that are of little value. When patients respond to combination therapy, it is never clear which agent or agents are working. Although all of the agents in any combination could be beneficial, it is also possible that one or more agents are of no value.

When single agents are used sequentially, it is important for patients to understand that if a first agent is ineffective, a second can be substituted. In many cases, the decision is not whether an agent should ever be used, but rather, when to use it.

Many Unanswered Questions About Trastuzumab

The authors review the findings from the recent trials of trastuzumab. Unfortunately, these trials only begin to answer the many questions about how to integrate this new therapy into the care of women with metastatic breast cancer. Trastuzumab is active as a single agent, and, when used together with paclitaxel (in patients whose tumors overexpress HER-2/neu), the combination results in a higher response rate than that seen with paclitaxel alone.

It remains unclear whether this enhanced activity represents true synergy. If the responses are only additive, are patients better off receiving combination therapy, or could they do equally well and perhaps experience less toxicity if trastuzumab and paclitaxel were administered sequentially? If there is true synergy, does this mean that a patient who has developed disease progression on paclitaxel alone would have a better response to paclitaxel plus trastuzumab than to trastuzumab alone?

Many other questions beg for answers. How long should trastuzumab be continued in a responding patient? Given the low toxicity of this monoclonal antibody, it is possible to continue treatment for a very long time, but this comes with a greater potential for toxicity and higher cost. What is the role of trastuzumab in the adjuvant setting? Finally, how can HER-2/neu positivity best be determined?
so that the specificity and sensitivity of trastuzumab are optimized? It will be important to address these issues and others relating to the optimal use of trastuzumab. Additional clinical trials will need to be designed, conducted, and analyzed before we have answers to the questions that clinicians face on a daily basis.

In the meantime, it will be important for physicians to use trastuzumab thoughtfully and appropriately. Although it appears to be well tolerated and is clearly one of the most exciting therapies for breast cancer in recent years, trastuzumab is not completely devoid of toxicity, and there is almost always some potential for harm with the use of any new agent.

**A Better Fluorouracil?**

Fornier and colleagues also review the recent studies that led to the FDA approval of capecitabine (Xeloda). Although fluorouracil (5-FU) is an old drug that has largely lost its place in doxorubicin-based regimens, the new oral 5-FU analogs may bring this class of agents back into the mainstream.

Both capecitabine and two agents currently in clinical trials (uracil-tegafur [UFT] and eniluracil) appear to mimic a continuous infusion of 5-FU, but with the ease of oral administration. Just because these agents are administered orally, however, does not necessarily mean that they are without any toxicity. Indeed, toxicity can be a serious problem, particularly if patients are not monitored closely and instructed to discontinue drug treatment if specific toxic effects develop. Despite this issue, as well as concerns about compliance, patients have clearly indicated a strong preference for oral anticancer agents,[4] and capecitabine now provides a reasonable alternative to other intravenous chemotherapeutic agents. Time will tell whether these agents lead to a reappearance of 5-FU in the adjuvant setting.

**Meeting Abstracts: The Need for Caution**

In this day of instantaneous access to information, it is hard to know how quickly new findings should be translated into clinical practice. While no one wants to deny patients treatments that may be helpful, it is important to recognize that many of the studies reviewed by Drs. Fornier, Munster, and Seidman have been presented only in abstract form. It is all too common for response rates and survival statistics (as well as toxicity reports) to change between the time a presentation is made at a national meeting and the manuscript's publication in a journal. The process of peer review is essential.

Yet rapid access to new drugs is very important to patients and to the clinicians who care for them. Increasingly, treatments may become commercially available before the final manuscript is published. In these situations, questions about the optimal use of a new agent will abound and further research will be needed.

There are no easy answers, but as we enter a new era of greater opportunity for the patient with advanced breast cancer, it is more important than ever that we thoughtfully evaluate the evidence for each and every new treatment and carefully integrate these new therapies with the best of the old.

**References:**


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