Current Status of Salvage Chemotherapy for Refractory Advanced Breast Cancer

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The definition of refractory advanced breast cancer remains elusive. Because of different definitions of objective response, frequent lack of precision in defining the number of prior chemotherapies, and differing interpretations

Introduction

In this era of cost containment, the benefits of all therapies are under intense scrutiny. In breast cancer management, the definitions of refractory advanced breast cancer and of its management are controversial. For the purpose of this article, refractory advanced breast cancer is partially and arbitrarily defined as primary or acquired resistance to hormonal therapies, anthracycline resistance, and failure of some otherwise undefined number of prior cytotoxic chemotherapeutic regimens. Attempting to determine the number of prior chemotherapeutic regimens that help to define refractory advanced breast cancer is both an interesting and often frustrating exercise in literature review.

To establish a frame of reference, what is known about the median survival from first relapse (MSFR) of patients with breast cancer must be explored. In a recent review of this topic in the context of presenting statistics from the University of Miami [1] (in which the overall MSFR of 26 months was similar to that in most reports in the literature), the most striking finding was the variability in MSFR, which depended on patient characteristics (Table 1). By combining these characteristics into prognostic categories, patient subgroups with a MSFR ranging from 15 to more than 90 months were defined (Table 2). Thus, when reviewing the literature on survival after any therapeutic intervention, it must be considered that such survival statistics are dependent on the heterogeneity of the population in question.

Difficulties With Response Rates

Other problems inherent in this literature review stemmed from an overreliance on response rates, which may be a relatively poor surrogate for clinical benefit. A significant percentage of women with metastatic breast cancer do not have bidimensionally measurable disease, and a large number of women have bony metastases that are difficult to evaluate. This frequently leads to defining "response" in populations of patients with lung, soft-tissue, and liver metastases, with the overall conclusion being that bony metastases "respond" poorly to treatment. Many medical oncologists believe that time from initiation of treatment to time of clear-cut tumor progression, or the "time to treatment failure" from any cause, might be a better end point than response rate. Howell et al [2] and Robertson et al [3] have suggested that disease stability lasting longer than 5 or 6 months should be considered similar to an objective response.

Different definitions of response have been applied to different clinical trials, with resultant discordant "response rates" for similar regimens in similar clinical circumstances. A recent phase II trial of medroxyprogesterone for metastatic breast cancer reported an objective response rate of 38.6% [4]. In contrast, two major, randomized, phase III trials of megestrol acetate vs the new aromatase inhibitor, anastrozole (Arimidex), yielded response rates of approximately 10% for both agents [5]. In the latter trials, the stringent International Union Against Cancer (UICC) response criteria were used. In these trials, adding patients with stable disease for longer than 24 weeks to the "responders" probably provided a more realistic assessment of clinical benefit, approximating the 30% rate expected from second-line hormonal treatment. As the definition of antitumor response becomes more stringent for quantitative purposes, it is important not to lose sight of the major goals of treatment: palliation, clinical benefit, and survival.

Similar problems exist with other tumor types. In lung cancer, the Eastern Cooperative Oncology...
Group conducted a study demonstrating that carboplatin (Paraplatin) resulted in the lowest response rate and the longest median survival among several different regimens tested [6] in pancreatic cancer, a new term, "clinical benefit response"[7], as well as an analysis according to that definition, has gained Food and Drug Administration (FDA) approval for gemcitabine (Gemzar), even in the face of low objective response rates. Perhaps, this encouraging precedent will lead to acceptance of alternative end points that more realistically reflect clinical benefit.

Other problems in this literature review stemmed from the different definitions of "heavily pretreated" used in various series. It was frequently impossible to determine individual response rates for second-, third-, or fourth-line therapies. In addition, information on anthracycline resistance was either impossible to disclose or was complicated by different definitions. Finally, in terms of survival durations, many articles cited medians, whereas others cited survival rates for responders and nonresponders; in some series, "stable" patients were combined with responders, and in others, they were grouped with nonresponders.

With these inherent problems in mind, this article will now endeavor to make some sense of the confusing literature on "salvage chemotherapy" for refractory advanced breast cancer.

**First- and Second-Line Chemotherapeutic Regimens**

In the United States, many first- and second-line chemotherapeutic regimens include combinations, such as cyclophosphamide, methotrexate, fluorouracil (CMF) or cyclophosphamide + doxorubicin (Adriamycin) ± fluorouracil (CA ± F)[8,9], with paclitaxel (Taxol) used mostly as second-line (or third-line) treatment. In Europe and Canada, other commonly used first-line regimens substitute epirubicin for doxorubicin; in addition, the mitomycin, methotrexate, mitoxantrone (MMM) combination is widely used as an alternative first-line regimen.

Commonly accepted "response rates" are in the 50% to 60% range for first-line therapy, with low complete response rates approximating 10% and response durations (depending on their definitions) approximating 8 months. Standard second-line chemotherapeutic regimens produce reasonably consistent response rates, which vary from 35% to 45% for patients in whom first-line, nonanthracycline-containing regimens failed (Table 3) [9-13] to 20% to 27% for patients in whom an anthracycline-containing regimen (Table 4) failed [14-16].

Among the newer agents, vinorelbine (Navelbine), at 30 mg/m²/wk, has produced an objective response rate of 32% as second-line therapy in patients in whom nonanthracycline regimens failed in an American trial [13], with higher response rates reported from Europe. Response rates with paclitaxel have been highly variable (32% to 62%), depending on the dose and schedule employed, even when it was used as first-line treatment of metastatic breast cancer (Table 5) [13,17-22]. In a single pure second-line trial by Seidman et al [23] using 250 mg/m² of paclitaxel given as 24-hour infusions with granulocyte colony-stimulating factor (G-CSF, filgrastim [Neupogen]) support, the response rate was 44%, with little difference between anthracycline- and nonanthracycline-resistant patients. Lower doses and shorter durations of paclitaxel therapy appear to yield response rates similar to those of vinorelbine therapy in previously treated patients [20,24,25].

Results for the taxanes (Table 6) [26,27] and vinorelbine (Table 7) [28-31] as second-line therapy for patients in whom anthracycline treatment has failed currently seem to favor the taxanes, but controlled, randomized trials in this subset of patients are needed to clarify this issue definitively. To date, the best results seen for the taxanes in anthracycline-resistant patients are with 96-hour paclitaxel infusions [26] or 1-hour docetaxel (Taxotere) infusions [27].

**The Controversy Surrounding Salvage Chemotherapy**

It seems that most clinicians would accept that first-line chemotherapy with response rates of 50% to 60% and survival longer than 1.5 years is generally worthwhile for patients with metastatic breast cancer. In addition, the population of patients with response rates of 35% to 45% for second-line therapy in whom nonanthracycline-containing first-line regimens failed should also be considered for treatment.

The use of second-line therapy for patients in whom first-line, anthracycline-containing regimens failed is controversial. Perhaps, it was this group that led to pessimism on the part of oncologists in Maryland; during a survey, these oncologists indicated that although they used second-line chemotherapy 74% of the time, they did so without much enthusiasm. In their commentary on these results, Benner et al [32] suggested that "standard chemotherapy be stopped after breast cancer fails to stabilize or respond on a standard regimen." They stated that "the frequent utilization of second-line regimens probably reflects an effort to offer marginal regimens to patients who want..."
them." This conclusion appears to be supported by Porkka et al [14] in a wellwritten article from Finland. Although 24% of their patients responded to second-line treatment after first-line anthracycline failure, only 10% of these patients had a time to treatment failure of longer than 6 months. In addition, they found that no patient treated with a third salvage chemotherapeutic regimen responded. They concluded that "the value of offering more than two salvage chemotherapy programs to an unselected group of patients is questionable." Undoubtedly, the findings of Benner's [32] and Porkka's [14] groups will be widely cited by managers of health maintenance organizations, as guidelines are written for the purpose of cost containment. In contrast, this degree of therapeutically nihilism comes at a time when a wide variety of potential salvage regimens are available (Table 8) and an unprecedented number of new investigational drugs with proven effectiveness for metastatic breast cancer are under development (Table 9). The problem is compounded by the general unavailability of stringently controlled trials to define the value of third-line and fourth-line (or higher level) therapies in patients with metastatic breast cancer. Clinicians are faced with a large number of small, uncontrolled trials often citing results at variance with the existing bias that third-line (or higher level) chemotherapy is generally ineffective.

'Standard' Regimens for Refractory Advanced Breast Cancer

Two major "standard" regimens have been used as third-line (or higher level) chemotherapy for refractory advanced breast cancer. The first of these regimens, mitomycin with a vinca alkaloid, has been used for 2 decades, most commonly in anthracycline-refractory patients. Table 10 summarizes several series [11,12,16,33-39]. In general, response rates have exceeded 20%. In the series by Perrone et al, [38], even though the response rate was low, overall survival was reasonably good. In the series by Benefrio et al [39], a dose of only 6 mg/m² of mitomycin was used. In the Ingle et al series [11], vincristine, generally considered to be less effective in breast cancer than some of the other vinca alkaloids, was used. Another frequently used salvage regimen consists of 5-fluorouracil, either by continuous infusion or modulated with leucovorin. Table 11 presents data summarized by Lokich and Anderson.[40,41] Two additional review articles on this topic have also been published [42,43]. Again, response rates seem generally favorable and are approximately 28%, usually for "heavily pretreated patients." Table 12 summarizes the relatively rare studies devoted to third-line therapy. Again, except for the previously discussed study by Ingle et al [11], the response rates of 31% to 41% are respectable and raise questions about the conclusions of Benner et al [32] concerning the value of third-line chemotherapy for the management of metastatic breast cancer.

The Role of Salvage Therapy

In this era of managed care, many organizations are seeking reasons to restrict therapy when the expectations of such treatment are "limited." Although Benner's [32] and Porkka's [14] groups would limit salvage chemotherapy for metastatic disease to, at most, two forms of chemotherapy, the data previously presented in Tables 10, 11 & 12, as well as unpublished personal observations over 20 years devoted to the practice of breast medical oncology, point to a less nihilistic conclusion about "salvage" therapy for refractory advanced breast cancer. Table 13 provides some intriguing comparisons with other disease entities [46,47]. Thus, although few clinicians would challenge the use of first-line chemotherapy for patients with non-small-cell cancer of the lungs or cancer of the colon, the use of third-line chemotherapy for patients with breast cancer is being questioned, despite similar results in terms of both response rates and median survivals. With all the available agents and regimens for salvage therapy, well-controlled trials of third-line (and higher level) chemotherapy are now needed. These trials are necessarily more complex because of the wide variability of preceding therapies. Philosophically, my approach to treatment of refractory advanced breast cancer utilizes regimens that will maximize quality of life without substituting the toxic side effects of aggressive chemotherapeutic regimens. Even in the advanced stages of this disease, many women remain concerned with the problem of nausea and alopecia; hence, regimens including vinorelbine or fluorouracil (5-FU) alone or in combination are useful. Gemcitabine could well emerge as an important palliative drug in breast cancer management, and exciting preliminary results using HER-2/neu antibody therapy could point to new noncytotoxic chemotherapeutic directions. Two other combinations that I have used effectively with little toxicity have been a mitoxantrone, 5-FU, and leucovorin regimen given on a day 1 and 8 schedule [48] and a Memorial Sloan-Kettering Cancer Center salvage regimen. The latter uses moderately high-dose methotrexate on day 1 followed by...
leucovorin rescue and 5-FU on day 2.

Among the wide variety of salvage programs available, platinum-based chemotherapeutic regimens and docetaxel are seldom used because of their toxicity profiles. In contrast, cisplatin and docetaxel should be intensively studied within first-line metastatic disease protocols and as part of potentially "curative" strategies in the adjuvant setting.

In clinical situations, it is unusual for patients with refractory advanced breast cancer to choose hospice care when there are so many therapeutic options available that hold some hope (albeit modest) for induction of antitumor response, palliation of symptoms, and prolonged survival. Patients almost always have social landmarks (upcoming weddings, births, graduations) that lead them to opt for attempts at active antitumor palliative care as opposed to hospice care.

**Comprehensive Cancer Research Group, Inc.**

This South Florida research group provides the research infrastructure for regional private practicing oncologists interested in having access to clinical trials for their patients. **Table 14** provides the current first-line protocol flow for our Comprehensive Cancer Research Group, Inc. (CCRGI). This first-line program may very well be unique with the availability of seven first-line chemotherapeutic programs. Protocol niches have been developed to cover most clinical situations. The high-dose Adriamycin/cyclophosphamide program, with or without interleukin-6 (IL-6) for platelet support, is available for neoadjuvant therapy.

The first-line Adriamycin/cyclophosphamide ± HER-2/neu antibody trial is for patients desiring standard anthracycline-based, first-line therapy. For the 70% of patients whose tumors do not express the HER-2/neu antigen, Adriamycin/cyclophosphamide is randomized against losoxantrone plus cyclophosphamide. For patients with no measurable disease, fluorouracil, Adriamycin, cyclophosphamide (FAC), with or without dexrazoxane (Zinecard), is available. In contrast to patients willing to accept aggressive anthracycline-based, first-line therapies, others would prefer exchanging a few percentage points of response for a better quality-of-life regimen. For such women, single-agent vinorelbine for patients older than age 60 and single-agent gemcitabine for patients younger than age 60 are available. Each of these single agents induces response rates of 35% to 40%, with 8-month remission durations, but without significant hair loss or other subjective side effects that frequently limit the tolerability of the more standard regimens. For women who absolutely refuse any form of cytotoxic chemotherapy and for women who have HER-2/neu antigen-positive tumors, an antibody trial is available.

**Second-Line CCRGI Program**—CCRGI's second-line program evaluates different schedules of paclitaxel administration. For third-line therapy, a phase II trial of the HER-2/neu antibody for eligible patients is offered.

CCRGI's program is contrasted with a more conventional treatment flow, which is depicted in **Table 15** [8,9]. Thus, a reasonably common sequence of treatments would start with cyclophosphamide, methotrexate, fluorouracil (CMF); move to vinblastine, Adriamycin, thiopeta, Halotestin (VATH) or some other anthracycline-based regimen; and be followed by paclitaxel (third-line), mitomycin plus vinblastine (fourth-line), and then some form of infusional or leucovorin-modulated fluorouracil regimen. CCRGI's standard flow would be similar to this one, except that it would start with an anthracycline.

**CCRGI'S Quality-of-Life Protocol**—CCRGI's quality-of-life protocol flow would start with vinorelbine or gemcitabine, then move to a day 1 and day 8 mitoxantrone, 5-fluorouracil, and leucovorin regimen [48], and be followed by a phase II trial of the HER-2/neu antibody for women who express this antigen or a vinorelbine/fluorouracil regimen (if first-line therapy had been gemcitabine). If vinorelbine had been used as a first-line agent, either CMF or the Memorial Sloan-Kettering Cancer Center salvage regimen (moderately high-dose methotrexate on day 1 followed by leucovorin rescue and fluorouracil on day 2) is a reasonably well-tolerated alternative third-line program. For fourth-through sixth-line therapy, single agents, such as low-dose weekly infusional doxorubicin, mitomycin, or infusional or leucovorin-modulated fluorouracil, might be offered.

**References:**
3. Robertson JF, Williams MR, Todd J, et al: Factors predicting the response of patients with advanced...

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