Survival of Patients with Metastatic Breast Cancer Treated with Either Combination or Sequential Chemotherapy

A Western Cancer Study Group Project


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ABSTRACT

One hundred twenty-one patients with metastatic adenocarcinoma of the breast were randomized to concurrent combination therapy or single-drug chemotherapy administered sequentially. Although response frequency and duration of response were significantly increased in patients receiving the combination regimen, survival was not significantly prolonged when compared to those receiving sequential treatment. For the 69 patients free of liver metastasis, median survival was comparable in both treatment arms (14.4 months sequential versus 12.8 months combination). These results indicate that a large subset of patients with metastatic breast cancer may benefit from less aggressive therapeutic regimens. Furthermore, these results illustrate that conclusions of chemotherapy trials in breast cancer based only on response frequency and duration of response represent preliminary results subject to change when final survival information becomes available.

INTRODUCTION

Combination chemotherapy trials for patients with advanced breast cancer have been reported for the past 15 years (3, 5, 7). During this time, many studies have documented an increased response frequency for patients treated with concurrently administered multiple-drug treatment regimens when compared historically to results achieved with single agents (3, 6). However, prolongation of survival by combination chemotherapy when compared to single-drug treatment has yet to be convincingly demonstrated. Even with regard to response frequency, controlled trials have not consistently reported superiority for concurrent combination treatment.

Lemkin and Dollinger (9) reported nearly identical response frequency for 5-FU treatment when compared to a 5-drug combination (30 versus 29%, respectively). Similarly, Rubens et al. (12) reported similar response frequency and survival when comparing cyclophosphamide alone to a 4-drug combination in patients with advanced breast cancer. The Eastern Cooperative Oncology Group compared melphalan alone versus a cyclophosphamide mehtotrexate-5-FU combination. Significantly increased response frequency (53 versus 20%; p < 0.05) was reported for the combination, but again without significantly increased overall survival (2). In a recent report, Mouridsen et al. (11) compared cyclophosphamide to a 5-drug combination. In this trial, response frequency of the combination was superior (63 versus 25%; p < 0.05); however, survival information was not reported. The 4 studies mentioned above compared the combination treatment to single-drug therapy without control over subsequent treatment given after removal from study.

Two studies have investigated aspects of combination versus sequential chemotherapy in metastatic breast cancer. Baker et al. (1) randomized between the combination of 5-FU, cyclophosphamide, and vincristine versus sequential use of the same drugs. Both the response frequency (53% sequential versus 45% combination) and the median survival (13 months sequential versus 7 months combination) were superior in the sequential single-agent arm. Smalley et al. (13) reporting for the Southeastern Cancer Study Group, found that, although a 5-drug combination produced more responses than did the same drugs given sequentially, the overall survival curves were not significantly different in the 2 arms.

The present Western Cancer Study Group protocol was designed to further investigate sequential versus combination therapy in metastatic breast cancer. The principal purpose was to determine whether a regimen involving 5 drugs given sequentially at the time of treatment failure would prolong the survival of patients with metastatic breast cancer when compared to the same 5 drugs given as a concurrent combination.

MATERIALS AND METHODS

One hundred twenty-six patients with metastatic breast carcinoma were entered on this study by members of the Western Cancer Study Group from February 1971 until November 1973.

Patient eligibility factors included the following: (a) histologically confirmed breast carcinoma with measurable disease
parameter; (b) no prior cytotoxic chemotherapy; (c) all patients either resistant to hormonal manipulation or had rapidly pro-
gressive disease; (d) no evidence of severe renal impairment
(creatinine > 0.02 g/liter) or severe liver function impairment
(bilirubin > 0.02 g/liter).

Pretreatment studies included physical examination, chest
X-ray, bone X-ray survey, liver scan, bone marrow aspiration
and/or biopsy, electrocardiogram, and routine biochemical
and hematological determination.

The established response criteria of the Western Cancer
Study Group were used. Responses were classified as: 1-C,
complete disappearance of all measurable lesions with the
appearance of no new lesions for ≥1 month; 1-B, reduction in
tumor mass ≥50% of the cross-sectional area of all measurable
lesions with the appearance of no new lesions for ≥1 month.
Minor changes, no change, or progression of any measurable
lesions during therapy are considered as no response. Patients
were randomly assigned by the Statistical Analysis Center to
receive either combination or sequential chemotherapy.

The combination regimen consisted of: cyclophosphamide,
2 mg/kg/day p.o.; 5-FU, 15 mg/kg every 2 weeks i.v. begin-
ning on Day 1; methotrexate, 30 mg/sq m every 2 weeks i.v.
beginning on Day 8; prednisone, 0.5 mg/kg/day p.o.; triiod-
othyronine, 0.005 mg daily. The patients in the single-agent
arm received the above drugs in the same dosages given
sequentially. 5-FU was given weekly for a minimum of 4 weeks.
If no tumor response was seen in that time or failure occurred
after initial response, the patient then received cytoxan p.o.
daily. After 4 weeks with no demonstration of tumor response
or upon failure after response, the patient received triiodothy-
rionine plus prednisone p.o. daily for a minimum of 6 weeks.
Again, with no response or on failure of response, methotrexate
was begun and was given i.v. weekly for a 4-week minimum
trial. In both arms, therapy was continued until disease pro-
gression occurred. All patients were followed until death. All
subsequent chemotherapy given after removal from study was
recorded.

RESULTS

Sixty-three patients were entered on both the combination
and sequential arms. Sixty-one patients in the combination arm
and 60 patients in the sequential arm were evaluable for toxicity
and response. All 5 unevaluable patients received concomitant
hormonal therapy at the time of entry on study. Five patients in
the sequential arm did not receive cyclophosphamide as their
second chemotherapy drug experience as called for in the
protocol. For the survival analysis, these 5 patients were con-
sidered to be removed from study alive at that point. They are
included in the evaluation for toxicity and response.

The patients randomized to each of the 2 regimens were
comparable with regard to length of disease-free interval, met-
astatic pattern, and menopausal status (see Table 1). At the
time of analysis, over 4 years had passed since entry of the
last patients. At present, 113 of the 121 evaluable patients are
dead. The last entered patient is now in the 52nd month of
observation. The survival curve of all study patients is shown
in Chart 1. Although median survival was somewhat longer for
the patients receiving combination treatment (14.8 months
versus 11.4 months), life table analysis demonstrated no sig-
ificant difference in survival between the 2 treatment arms.
Chart 1 also illustrates the projected survival curve generated
by an analysis of the survival information available 12 months
after the entry of the last patient on study. That analysis, done
at a time when 51 patients had died, indicated that the survival
difference between the 2 treatment arms would be significant
(p < 0.05); however, this projected difference was not sup-
sported when the patient's actual survival information was ob-
erved. Median survival of patients treated with the combination
regimen was over 100 days longer than that of patients treated
with the sequential regimen when the CNS, lungs, or liver were
involved with tumor. In the case of liver involvement, the differ-
ence in survival achieved statistical significance (median, 15.2
months for combination versus 8.0 months for sequential; p <
0.04). For the large group of patients without liver metastasis,
treatment with the sequential regimen resulted in comparable
survival at all time periods compared to treatment with the
combination regimen (Chart 2). Thirty patients did not have
cNS, lung, or liver metastases. In this group of patients with
limited disease, only 1 of 30 patients died in the first 7 months
of study regardless of treatment arm.

The response to the 2 regimens is shown in Table 2. Fifty-six
% of patients treated with the combination regimen achieved
either a 1-B or 1-C response. Of the patients treated with the
sequential regimen, 52% had a 2-B or 2-C response.

Table 1

<table>
<thead>
<tr>
<th>Metastatic sites (%)</th>
<th>Free interval &lt;1 yr (%)</th>
<th>Menopausal status pre + &lt;1 yr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Bone</td>
<td>Liver</td>
</tr>
<tr>
<td>Combination (61)⁴</td>
<td>11 (7)</td>
<td>57 (36)</td>
</tr>
<tr>
<td>Sequential (60)</td>
<td>10 (6)</td>
<td>64 (38)</td>
</tr>
</tbody>
</table>

⁴ Numbers in parentheses, number of patients.
response to 5-FU responded to subsequent single-agent therapy. Duration of response was significantly greater in the combination-treated patients (median, 13.4 versus 7.7 months; \( p < 0.01 \)). The survival of patients demonstrating a 1-B or 1-C response was similar in both arms (median, 18.0 months for combination versus 17.6 months for sequential). The chemotherapy given after removal from study was similar in both arms and illustrated in Table 3.

Toxic effects of treatments are illustrated in Table 4. Leukopenia and mucositis were more common in patients receiving the combination treatment, whereas gastrointestinal toxicity was similar with the 2 regimens. Two treatment-related deaths occurred in the combination arm. There was no correlation between degree of leukopenia and survival in either treatment arm.

**DISCUSSION**

The current prospective study compared concurrent combination versus sequential chemotherapy for patients with metastatic breast cancer. Although response frequency and duration of response were increased in patients receiving the combination regimen, survival was not significantly prolonged in this group of patients when compared to those receiving the single-agent sequential treatment. It was apparent that the combination therapy regimen was beneficial to patients with metastases in life-threatening areas (CNS, lung, and liver). However, for patients with metastatic disease not involving these regions, survival at all time periods was slightly superior in the sequential treatment arm. The fact that only 1 of 30 patients without liver, lung, or CNS metastases died during the first 7 months after study entry illustrates that there is a subset of patients who will experience prolonged survival with or without concurrent combination therapy. These data are quite comparable to those reported by the Southeastern Cancer Study Group for their combination versus sequential trial in metastatic breast cancer. In that trial, a continuous 5-drug combination resulted in significantly increased response frequency (46% combination versus 18% sequential; \( p < 0.05 \)), no significant difference in the overall survival curves, and an observation that approximately one-third of the patients experienced prolonged survival regardless of therapy (13). At the time of that report, 24% of the sequential and only 14% of the combination groups were still alive and under follow-up. Thus, both cooperative group trials involving sequential single-agent chemotherapy identified a subset of patients who experienced prolonged survival on such nonaggressive regimens (4).

It should be noted that the projected survival curve which grew out of an analysis completed 12 months after the last patient’s entry on study demonstrated a significant survival advantage to the combination regimen over the sequential arm (Chart 1). By 14 months after the completion of the study, this significant difference was lost, and the final survival curves were similar in both arms. These results illustrate the internal bias inherent in life table analyses based on incomplete survival information for studies of breast cancer. Such analyses are likely to favor the more aggressive therapy since only the effects of treatment on the patients at risk of dying in the early interval will be seen. For patients with breast cancer, this means either aggressive disease or disease involving vital organs. These patients must show an early response to therapy or they will die and therefore be reflected in early survival.
analyses. As seen in this study, however, a subset of patients can be identified who are unlikely to die during the first months of study regardless of whether they received the combination or single-agent sequential regimens. However, the fact that the sequential regimen was as effective for this set of patients would not be apparent in survival analyses performed during early periods of follow-up when all such patients remain alive. The problem of extrapolation of early response information to overall survival can also be seen by examining the relationship between response frequency, duration of objective response, and survival. In the current study, although combination therapy resulted in significantly increased response frequency (56 versus 32%; p < 0.05) and response duration (13.4 versus 7.7 months; p < 0.05), nonetheless, survival was not significantly prolonged by the combination regimen (14.8 versus 11.4 months). The Eastern Cooperative Oncology Group comparison of cyclophosphamide-methotrexate-5-FU versus melphalan showed a similar pattern. Combination therapy that in this study resulted in increased response frequency (55 versus 20%) and duration of objective response (9.1 versus 5.0 months) but without significantly prolonged survival when the 2 treatment groups were compared throughout the total treatment periods.

Triiodothyronine was utilized in this study since previously this agent had been shown to increase the response frequency of patients with breast cancer treated with steroids from 5 to 28% (10, 14). The response frequencies seen for the combination regimen in this study are similar to those reported for the same agents in many other studies not involving thyroid treatment (3, 13). Therefore, the ultimate role of triiodothyronine in the treatment of breast cancer remains to be determined.

The initial preliminary report of this study (8) was interpreted to support the superiority of combination therapy over a sequential approach (3). Now we illustrate that interpretations based on response frequency, duration of response, and preliminary projected survival curves in studies of patients with breast cancer are subject to change when final survival information is available. Therefore, a long-term and complete follow-up is essential to assess the full impact of any chemotherapy regimen in breast cancer.

In summary, a randomized trial of combination versus sequential chemotherapy for patients with metastatic breast cancer demonstrated no significant difference in survival in the 2 treatment arms despite increased response frequency and response duration in the combination arm. Furthermore, it appears that some patients without vital organ involvement can experience comparable survival when treated with sequential chemotherapy. These data suggest that more than one treatment strategy will be required to optimize survival of patients with metastatic breast cancer. Future modifications of the sequential single-agent approach to treatment might include use of a fixed rotation of single agents (instead of the treatment until failure approach described in this report) and escalation of dosage for such single agents as are reported to have a favorable dose-response relationship in this disease.

REFERENCES

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