Significance of Relapse after Adjuvant Treatment with Combination Chemotherapy or 5-Fluorouracil Alone in High-Risk Breast Cancer

A Western Cancer Study Group Project


ABSTRACT

Beginning in 1974, patients undergoing mastectomy at high risk for recurrence (≥4 nodes positive; median, 9.4 positive; range, 4 to 28) were randomized after stratification for menopausal status and radiotherapy to receive either 5-fluorouracil (5-FU, 500 mg/sq m i.v. every week) or cyclophosphamide, 400 mg/sq m; methotrexate, 30 mg/sq m; and 5-FU, 500 mg/sq m (CMF; all given i.v. every 2 weeks) in a 12-month program. All 62 patients remain evaluable with median follow-up now exceeding 70 months (range, 60 to 80 months). CMF significantly prevented early disease recurrence (97% relapse free on CMF versus 75% on 5-FU at 12 months; p < 0.05) and demonstrated survival advantage during the initial 40-month follow-up. This significance was subsequently lost, and the percentages of relapse free and overall survival after 70 months are:

<table>
<thead>
<tr>
<th>Relapse Free</th>
<th>Survival</th>
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<tbody>
<tr>
<td>5-FU</td>
<td>61</td>
</tr>
<tr>
<td>CMF</td>
<td>61</td>
</tr>
<tr>
<td>5-FU</td>
<td>47</td>
</tr>
<tr>
<td>CMF</td>
<td>47</td>
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The apparently paradoxical relationship between relapse and survival on the 5-FU arm was related to survival after recurrence. Survival after recurrence was significantly longer on the 5-FU compared to the CMF arm (median of >38 versus 10 months, respectively; p < 0.01). These results suggest (a) long-term survival in adjuvant trials cannot be accurately predicted by short-term differences in relapse frequency, (b) survival after relapse may be influenced by the antecedent adjuvant therapy received, and (c) disease relapse does not necessarily preclude long-term survival.

INTRODUCTION

The goal of adjuvant chemotherapy administration following mastectomy in breast cancer is to improve overall patient survival. However, at present, adjuvant breast cancer trials are commonly interpreted using short-term alterations in disease relapse as a secondary endpoint (2, 12). In advanced breast cancer, data from 3 cooperative groups has suggested that improvement in response frequency, a commonly used end point for assessing chemotherapeutic effectiveness, may not be associated with long-term survival benefit (6, 7, 20, 21). In some cases, this result required years of follow-up to be appreciated (9). The length of the follow-up period required for accurate assessment of adjuvant breast cancer trials is not known since relatively little long-term survival information in patients receiving adjuvant chemotherapy is currently available. We now report the survival experience at a median of 70 months after mastectomy of patients treated adjuvantly in a randomized prospective trial with either combination chemotherapy using CMF® or single-agent therapy using 5-FU.

MATERIALS AND METHODS

Patients were entered on this study by members of the WCGS beginning in August 1974. All female patients who had a radical mastectomy (conventional or modified) for potentially curable breast carcinoma with 4 or more axillary nodes positive on histological examination were considered eligible for study provided they satisfied the following protocol requirements: (a) tumor confined to the breast or breast and axilla; (b) negative radiological studies (chest X-ray and bone scans); and (c) adequate bone marrow reserve as defined by a peripheral WBC greater than 4500/cu mm, platelet count greater than 150,000/cu mm, and blood urea nitrogen less than 30 mg/100 ml. There was no age limitation on patient entry. The following conditions made patients ineligible: (a) less than 10 ipsilateral lymph nodes available for pathological examination; (b) history other than infiltrating ductal or lobular carcinoma; (c) prior carcinoma in either breast; or (d) prior chemotherapy or hormonal therapy. Patients more than 6 weeks postmastectomy were also ineligible. Patients who received postsurgical chest wall and regional lymph node irradiation were eligi...
ble provided all other entry requirements were met.

Patients were stratified according to menopausal status and postsurgical radiotherapy. Patients were then randomized to receive either 5-FU alone or a 3-drug CMF combination. On the single agent arm, 5-FU at a dose of 500 mg/sq m was given every week. The CMF combination arm included cyclophosphamide (400 mg/sq m), methotrexate (30 mg/sq m), and 5-FU (500 mg/sq m) all given i.v. on an every-2-week schedule. This CMF regimen had previously received pilot evaluation in 18 patients with advanced breast cancer and resulted in a 56% objective response frequency. Both adjuvant regimens were given for a 12-month treatment period. Drug dose was adjusted for hematological toxicity: WBC greater than 3500/cu mm and platelets greater than 100,000/cu mm resulted in full dose; WBC greater than 1500/cu mm but less than 3500/cu mm and platelets greater than 50,000/cu mm resulted in 25% dose reduction; WBC less than 1500/cu mm or platelets less than 50,000/cu mm resulted in no drug administration until WBC reached 1500/cu mm and platelets reached 50,000/cu mm.

Follow-up evaluation of liver function tests and alkaline phosphatase was carried out every 3 months during the 12 months of treatment and subsequently at 6-month intervals. Chest X-ray and bone scan were repeated after 6 months and upon completion of treatment. After the 12-month treatment period, follow-up was at 3-month intervals. History and physical examination were rechecked at each visit, with chest X-ray and scans conducted as clinically indicated. All patients were followed until death. All chemotherapy or hormonal therapy given after disease relapse was recorded.

All patients who received one or more dose of chemotherapy were considered evaluable. The end points of study used for statistical analyses included the time from mastectomy until the first evidence of disease relapse (relapse-free interval) and the time from mastectomy until death (overall survival). Relapse-free interval and overall survival are depicted using standard life table methods (16). The estimate of probability of differences was carried out with the log rank test (18).

RESULTS

A total of 62 patients were entered on study and all remain evaluable for toxicity and response. Patients randomized to the 2 regimens were comparable with regard to median age, menopausal status, and postsurgical radiotherapy (Table 1). The median number of positive nodes was greater than 9 in both arms. Median follow-up now exceeds 70 months with all patients followed between 60 and 80 months from mastectomy.

The major toxic manifestation of the 2 adjuvant regimens was hematological. Although leukopenia less than 4000/cu mm was more frequent on the CMF arm (68% versus 26%; p < 0.05), few patients on either regimen experienced severe myelosuppression (Table 2). Gastrointestinal problems and hair loss were also somewhat more frequent in the CMF arm. No treatment-related deaths occurred as both regimens were well tolerated.

The dose level of chemotherapy administered as percentage of scheduled dose is given in Table 3. These values were calculated using the actual amount of drug scheduled for administration during that period. Within these levels, survival was not related to the dose level of chemotherapy administered. However, survival was significantly decreased (p < 0.05) for the relatively few patients who received less than 50% of the scheduled dose.

The short-term influence of CMF or 5-FU on the relapse-free interval of all patients is illustrated in Chart 1 and depicts results available in 1976 after 12 months median follow-up. CMF significantly prevented early disease recurrence (97% relapse free on CMF versus 75% on 5-FU at 12 months; p < 0.05) resulting in survival advantage during the initial 40 months of study. The current survival status of all patients at 70 months median follow-up is shown in Chart 2. Although survival on CMF was initially greater, subsequently this difference was lost as the survival curves crossed at 40 months. At present, survival is somewhat greater on the 5-FU arm (61% versus 47%; NS). Current survival of patients receiving or not receiving postsurgical radiotherapy is nearly identical (overall survival of 56% versus 55%; NS).

Both premenopausal and postmenopausal patients demonstrated a similar relationship between relapse-free interval and overall survival (Table 4). In all categories illustrated, the percentage of patients remaining relapse free was greater on the CMF arm with the difference in premenopausal patients being statistically significant (p < 0.05). However, overall survival in all categories was somewhat greater on the 5-FU arm. None of these differences in overall survival achieved statistical significance since, in all categories, an early survival advantage was seen with CMF treatment followed by long-term advantage to 5-FU treatment. Thus, despite more frequent disease relapse, survival was not decreased in the patients initially receiving 5-FU treatment.

The sites of relapse and category of therapy (chemotherapy, hormonal therapy, or radiotherapy) given following relapse were nearly identical in both arms (Table 5) with 75% of
patients receiving chemotherapy as their initial treatment after recurrence. The apparently paradoxical relationship between relapse-free interval and overall survival on the 5-FU arm can be explained by considering the survival of patients following disease relapse. As seen in Chart 3, the survival of patients receiving chemotherapy for relapse was significantly greater for patients who initially received 5-FU rather than CMF treatment (median survival from relapse of 38 months versus 10 months; \( p < 0.001 \)). In addition, there is the suggestion of a plateau in the survival curve which represents 9 patients who remain alive 40 to 68 months after relapse on the 5-FU arm.

The specific chemotherapy that patients on the 2 arms received following relapse is given in Table 5. The majority of patients relapsing on the CMF arm were treated with doxorubicin-containing combinations while 80% of patients relapsing on the 5-FU arm subsequently received either CMF or cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone combined chemotherapy with only a minority receiving doxorubicin. It is not possible to give precise data regarding response frequency to these regimens given after relapse since the majority of patients had major recurrence in the difficult-to-evaluate skeletal region. All patients who experienced greater than 36 months survival after relapse were initially on the single agent 5-FU arm but subsequently received combination chemotherapy as their first therapy after relapse.

**DISCUSSION**

This WCSG adjuvant trial compared combination treatment with CMF to single-agent treatment with 5-FU in breast cancer patients at high risk for relapse following mastectomy. The results at 70 months median follow-up indicate that although CMF influenced early disease relapse, long-term survival benefit was not seen. Discrepancy between long-term survival and short-term changes in relapse frequency has occurred in other breast cancer adjuvant trials with comparable long-term follow-up. For example, the Milan study (2) comparing CMF with no treatment initially reported (at 14 months median follow-up) a statistically significant decrease in disease relapse for patients with 4 or more nodes receiving CMF (92% versus 60%; \( p < 0.001 \)). However, overall survival at 5 years (3) for the CMF arm was nearly identical to the control arm (57% versus 56%; NS). Similar results (fewer early relapses without long-term survival benefit) occurred in postmenopausal patients receiving CMF in that trial. The National Surgical Adjuvant Breast and Bowel Project study comparing L-PAM to a control population also initially reported a highly significant decrease in disease relapse for the L-PAM arm, especially in premenopausal patients (12). However, no significant survival benefit was seen in this population after longer follow-up (13). Precisely the opposite results were seen in a Scandinavian trial reported by Nissen-Meyer et al. (17). Cyclophosphamide was not associated with a significant decrease in disease relapse during the first 4 years of observation compared to no chemotherapy controls; nevertheless, long-term overall survival was significantly greater for the patients receiving chemotherapy. Taken together with the current report, such results suggest that long-term survival in adjuvant breast cancer trials cannot be accurately predicted by short-term changes in relapse frequency.

The improved overall survival which was observed on the 5-FU treatment arm, despite an increased frequency of disease relapse, can be explained by the significantly increased survival...
of these patients following relapse. The plateau of the survival curve in patients relapsing after 5-FU adjuvant treatment suggests that disease recurrence following mastectomy may not necessarily preclude long-term survival. Our patients frequently relapsed in one site and may be comparable to the regionally treated Stage IV breast cancer patients who were given “adjuvant” chemotherapy by Blumenschein et al. (1). These patients also had a solitary site of recurrence and, following radiotherapy and combination chemotherapy plus immunotherapy, experienced long-term survival in some cases.

Many adjuvant trials have compared combinations with single-agent chemotherapy in breast cancer (11, 19, 22). However, the single agent utilized in previous comparisons has always been the alkylating agent L-PAM. Thus, in the current WCSG trial, the excellent prognosis after relapse of patients initially receiving 5-FU is not directly comparable to that of patients receiving either intensive combination chemotherapy or single alkylating agents as their adjuvant treatment. In any case, the better prognosis of patients initially receiving 5-FU rather than CMF suggests that survival after relapse may be significantly influenced by the adjuvant therapy received. This observation reinforces the need for long-term follow-up to accurately interpret any breast cancer adjuvant trials.

It is well established that disease relapse increases with the number of positive nodes (14). Thus, the patient population in this trial was at extremely high risk for disease relapse with a median of more than 9 nodes positive in both arms. Patients with 10 or more nodes positive rarely constitute more than 15% of adjuvant trials (4); however, in our study, nearly 50% of patients had greater than 10 nodes involved with tumor. A trial involving all node-positive patients would have to enter about 200 cases to include a comparable number of such high-risk patients.

The CMF regimen in this trial included the same 3 agents but with different dosage and schedule from that used by Canellos et al. (5) and Bonadonna et al. (2). The dosage of methotrexate and 5-FU scheduled for administration per cycle was lower (75% and 83%, respectively) than that used in the CMF of the Milan trial. However, the amount of drug actually administered was closely comparable to that given by Bonadonna and Valagussa (3) since a higher proportion of patients in the WCSG trial received ≥85% of their scheduled dosage. In the schedule used in this trial, all drugs were given every other week by the i.v. route. Thus, there is no question of compliance with a p.o. agent. The effectiveness of this CMF schedule in advanced breast cancer during pilot evaluation with an objective response frequency of 56% supports its comparability to CMF regimens used in other adjuvant trials.

One year of CMF adjuvant therapy has not been associated with long-term survival benefit in the multiple-node patient population at high risk for relapse in this and other trials (3, 15). However, several more intensive combinations have achieved results suggestive of benefit even in such groups as >10-node-positive (4, 15) and postmenopausal patients (4, 10, 15, 22). It will be interesting to follow the long-term survival of patients on these promising combination regimens to see whether such initial benefit is maintained.

In summary, the results of the current adjuvant trial suggest: (a) long-term survival in adjuvant trials cannot be accurately predicted by short-term changes in relapse frequency; (b) survival after relapse may be significantly influenced by the antecedent adjuvant therapy received; and (c) disease relapse following mastectomy does not necessarily preclude long-term survival.

REFERENCES

Survival after Relapse in Adjuvant Breast Cancer


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