EFFECT OF PSYCHOSOCIAL TREATMENT ON SURVIVAL OF PATIENTS WITH METASTATIC BREAST CANCER

DAVID SPIEGEL
HELENA C. KRAEMER
JOAN R. BLOOM
ELLEN GOTTHEIL

Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California; and Department of Social and Administrative Health Sciences, School of Public Health, University of California, Berkeley, California, USA

Summary The effect of psychosocial intervention on survival of 86 patients with metastatic breast cancer was studied prospectively. The 1 year intervention consisted of weekly supportive group therapy with self-hypnosis for pain. Both the treatment (n = 50) and control groups (n = 36) had routine oncological care. At 10 year follow-up, only 3 of the patients were alive, and death records were obtained for the other 83. Survival from time of randomisation and onset of intervention was a mean 36.6 (SD 37.6) months in the intervention group compared with 18.9 (10.8) months in the control group, a significant difference. Survival plots indicated that divergence in survival began at 20 months after entry, or 8 months after intervention ended.

Introduction

Many studies have demonstrated positive psychosocial effects of group therapy in cancer patients, including improvements in mood, adjustment, and pain. However, few studies have prospectively examined medical effects. In general, patients who receive psychotherapy survive longer. Our objective was to assess whether group therapy in patients with metastatic breast cancer had any effect on survival. This group intervention has been reported to improve the psychological well-being of such patients. We started with the belief that positive psychological and symptomatic effects could occur without affecting the course of the disease; we expected to improve the quality of life without affecting its quantity. Here we describe a 10 year follow-up of the effect of psychosocial intervention on disease progression and mortality.

Patients and Methods

Patients

Only subjects with documented metastatic carcinoma of the breast were included. 109 women were referred by their oncologists. Those patients who agreed were called upon by our research interviewers, who told them about the study and invited

T. MITSUDA AND OTHERS: REFERENCES—continued

TABLE I—DETAILS OF CONTROL AND INTERVENTION PATIENTS

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 36)</th>
<th>Intervention (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At initial diagnosis</td>
<td>49 (10.5)</td>
<td>49.9 (10.0)</td>
</tr>
<tr>
<td>At study entry</td>
<td>54.6 (10.2)</td>
<td>54.7 (9.9)</td>
</tr>
<tr>
<td>Married</td>
<td>26 (69%)</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumpectomy</td>
<td>6 (17%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Simple mastectomy</td>
<td>2 (6%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Modified radical mastectomy</td>
<td>11 (31%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>Radical mastectomy</td>
<td>17 (47%)</td>
<td>26 (52%)</td>
</tr>
<tr>
<td>Degree of metastatic spread*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft tissue</td>
<td>0.3 (0.5)</td>
<td>0.5 (0.6)</td>
</tr>
<tr>
<td>Vascular</td>
<td>0.3 (0.5)</td>
<td>0.3 (0.5)</td>
</tr>
<tr>
<td>Bone</td>
<td>0.4 (0.7)</td>
<td>0.3 (0.7)</td>
</tr>
<tr>
<td>Initial stage†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (8%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>II</td>
<td>18 (50%)</td>
<td>16 (32%)</td>
</tr>
<tr>
<td>III</td>
<td>5 (14%)</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>IV</td>
<td>7 (19%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>No of metastasies‡</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hours per week</td>
<td>1.7 (0.8)</td>
<td>1.6 (0.8)</td>
</tr>
<tr>
<td>Activity level</td>
<td>1.9 (1.1)</td>
<td>1.8 (1.1)</td>
</tr>
<tr>
<td>No of treatment courses at entry‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Oestrogen</td>
<td>0.0 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Androgen</td>
<td>0.0 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Steroid</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Irradiation</td>
<td>1 (1.0)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Days of irradiation</td>
<td>41 (7.89)</td>
<td>18 (8.24)</td>
</tr>
</tbody>
</table>

Mean (SD) or no. of cases.
*Spread of metastasis scaled as: 0 = no spread, 1 = one site, 2 = more than one site of a particular type, and 3 (bone only) = four or more sites.
†Ty for trend, p < 0.01.
‡Median (lower and upper quartiles = median except where indicated).
(Self-ratings 1-5.

them to participate. Of this group, 86 completed the first questionnaire, while 18 others refused to participate and 5 died before contact. After written informed consent was obtained (protocol approved by Stanford Human Subjects Committee), a battery of psychological tests was administered. The subjects were then randomly assigned to either the intervention or control groups, and initial follow-up was done every 4 months for a year. More subjects were randomly assigned to therapy (n = 50) than to control (n = 36) to ensure enough patients for group work. 14 subjects assigned to group therapy were too weak or ill at initial interview to participate; 6 died after entry but before the groups began and 2 others moved away. 12 subjects were lost from the controls; 4 were too ill to participate, 2 died, 4 refused to participate, and we were unable to contact 2. 30 of the 34 women in the intervention group and all 24 control women survived long enough to respond to at least one follow-up questionnaire during the year of study. During the first year there was no indication of improved survival in the treatment group; in fact, slightly more patients in this group died during this period (30 or 22%), while none in the intervention group died.

Survival time, obtained for all patients who entered the study, was based on state death records for 83 patients. All but 2 of these had breast cancer listed as the immediate or contributing cause of death. The 2 deaths not related to cancer occurred in the controls: 1 cerebrovascular accident and 1 suicide. We made phone contact with the 3 survivors. For other than the primary survival analysis, these 3 were treated as though their date of death was July 1, 1988, when all death records had been obtained. If there was any bias resulting from this decision, it would be in the direction of minimizing the impact of intervention, since all 3 were in the treatment group.

The two groups were similar at study entry except for a nearly significant difference in staging at initial diagnosis (tables 1 and 2). Staging information, based on medical records at study entry, was available for 70 of the 86 patients. Initial staging favoured the intervention group. Initial staging took place, on average, 59.2 (SD 7.8) months before the beginning of the study. Patients were not referred to us until they had metastatic disease. Since some studies show that staging is a predictor of survival, it could be that by chance the treatment sample had a better prognosis when initially diagnosed than the controls. We found, however, that initial staging was unrelated to survival from the time of randomisation until death. Nonetheless, staging was a control variable during analysis.

**Intervention**

The intervention lasted for a year while both control and treatment groups received their routine oncological care. The three intervention groups met weekly for 90 min, led by a psychiatrist or social worker with a therapist who had breast cancer in remission. The groups were encouraged to discuss the impact of breast cancer, and how to cope with it. At no time were patients led to believe that participation would affect their course of disease. Group therapy sessions were conducted in a relaxed manner and expressed their feelings about the illness and its effect on their lives. Physical problems, including side-effects of chemotherapy or radiotherapy, were discussed and a self-hypnosis strategy was taught for pain control. Social isolation was countered by developing strong support networks among members. Members encouraged another to be more assertive with doctors. Patients focused on how to manage the challenges of breast cancer so they could manage their lives.

**Analysis**

The analysis used Cox's proportional hazards model to examine whether intervention affected survival. This model was chosen so that we could assess the influence of treatment assignment over and above the effect of pre-randomisation prognostic variables by O'Brien's logit-rank procedure. The log-rank test was also used to ensure that main effect differences were significant although the hazards of survival differed. We also drew Kaplan-Meier plots, and used unpaired t, Wilcoxon's rank sum, and x² tests where appropriate.

**Results**

Most striking was the difference in survival from time of randomisation, when intervention began, until date of death. Survival time for the treatment group was significantly longer compared with controls (table 3 and figure). In addition the interval from first metastasis to death was significantly longer for the group randomised to treatment. Thus the intervention group lived on average twice as long as did controls.

Since initial staging differed, we examined whether the group randomised to treatment was not as ill and therefore survived longer. The following points make this unlikely: (1) all patients had metastatic disease at recruitment and

TABLE II—DISEASE COURSE PRE-ENTRY (MONTHS)

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 36)</th>
<th>Intervention (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial diagnosis to first metastasis</td>
<td>38 (44.9)</td>
<td>36 (35.6)</td>
</tr>
<tr>
<td>First metastasis to entry</td>
<td>24.4 (17.4)</td>
<td>21.9 (21.8)</td>
</tr>
<tr>
<td>Initial diagnosis to entry</td>
<td>62.3 (53.5)</td>
<td>58.0 (43.3)</td>
</tr>
</tbody>
</table>

Mean (SD).

47.6 months before the beginning of the study. Patients were not referred to us until they had metastatic disease. Since some studies show that staging is a predictor of survival, it could be that by chance the treatment sample had a better prognosis when initially diagnosed than the controls. We found, however, that initial staging was unrelated to survival from the time of randomisation until death. Nonetheless, staging was a control variable during analysis.

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Since initial staging differed, we examined whether the group randomised to treatment was not as ill and therefore survived longer. The following points make this unlikely: (1) all patients had metastatic disease at recruitment and
randomisation, and therefore had a fairly uniform prognosis; (2) there were no differences in other important prognostic variables; and (3) although initial staging was, as expected, significantly correlated with time from initial medical visit to date of first metastasis (Spearman’s $r = -0.42$, $n = 70$, $p < 0.0003$), this variable was not correlated with any survival variables, including the outcome variable that differentiated between treatment and control groups—ie, time from entry to date of death ($r = 0.03$, $n = 70$).

To address this potential problem directly, the between-group differences were examined controlling for initial staging. The difference in survival from randomisation to death between the treatment and control groups remained highly significant ($n = 70$, $p < 0.0001$). Staging had little influence on this survival variable ($p < 0.06$). Likewise the difference between the dates of metastasis and death remained significant ($p < 0.02$). In addition, examination of Kaplan-Meier curves for treatment versus control patients matched for initial staging revealed a pattern similar to that seen for the overall sample in the figure. Survival between intervention and control groups was different within each homogenous staging group. This analysis indicated that initial staging differences do not account for the observed differences in survival between the groups.

Although there were no significant differences between treatment and control groups in chemotherapy and irradiation before randomisation, we tested the significance of the main effect for survival while controlling for each of these variables with the O’Brien procedure, entering the medical treatment variable first and then group status. In each case the treatment/control difference held. Of most interest was the significance of the treatment/control difference in survival after entering those variables that were close to being significantly different: days of irradiation ($n = 69$, $p < 0.0005$) and androgen ($n = 86$, $p < 0.0004$) and steroid treatment ($n = 86$, $p < 0.0004$). Differences in time from first metastasis to death also remained significant with this analysis. Thus these variables do not account for the enhanced survival.

There was variation in attendance among those randomised to group therapy. Illness accounted for some of this variation. Indeed, 15 patients in the treatment group and 8 controls died during the year. Some other patients moved away or were reluctant to attend their group. To examine between-group differences among those patients who where more actively involved, we did the same Cox regression analysis on the 54 patients who completed both a baseline and at least one of the three follow-up questionnaires during the year. The difference in survival time from randomisation to death between treatment and control groups again remained significant ($p < 0.0001$), even when staging was controlled ($n = 42$, $p < 0.0001$), and when log-ranks were used ($p < 0.03$).

Discussion

Patients with metastatic breast cancer randomised to weekly group therapy for a year lived significantly longer than did controls, by an average of nearly 18 months. This difference was statistically and clinically significant. Our results are consistent with but greater in magnitude than those of Grossardt-Maticek et al., and overcome the problem of differences in time from initial diagnosis to study entry which limited the findings of Morgenstern et al. 7

In agreement with Cassileth et al.8 and Jamison et al.9 we found that a battery of extensive psychological assessments before intervention did not significantly predict survival. Indeed the only variable to affect survival time significantly was our complex psychosocial intervention. The effect of group interaction on longevity was not apparent in the year of intervention. Treatment and control groups did not diverge until about 8 months after the year was over (figure), which may be explained, as would the result of a somatic treatment, as a cumulative mild effect on time until death.

Our follow-up study was done to investigate whether psychosocial intervention, which significantly reduced anxiety, depression, and pain, would do so without having any effect on the course of the disease. We intended, in particular, to examine the often overstated claims made by those who teach cancer patients that the right mental attitude will help to conquer the disease. In these interventions patients often devote much time and energy to creating images of their immune cells defeating the cancer cells.10 At no time did we take such an approach. The emphasis in our programme was on living as fully as possible, improving communication with family members and doctors, facing and mastering fears about death and dying, and controlling pain and other symptoms. To the extent that this intervention influenced the course of the disease, it did not do so because of any intention on the part of the therapists or the patients that their participation would affect survival time.

What could account for the differences observed? Social support may be an important factor in survival.8-10 Even when matched for health habits, social relations affect survival.20,21 The provision of social support for isolated individuals under stress can improve health outcome.8 Social support is important in mediating how individuals cope with stress. For example, married cancer patients survive longer than unmarried patients.23 In our study there was a higher proportion of married patients in the control group (70% vs 57%). The fact that treatment patients had longer survival may indicate the efficacy of psychosocial intervention. One role of the group might have been to provide a place to belong and to express feelings.24 Clearly the patients in these groups felt an intense bonding with one another and a sense of acceptance through sharing a common dilemma. 1 patient with oesophageal strictures secondary to irradiation described her sense of estrangement
from the world; while struggling to swallow soup at a restaurant, she thought: "These people don't realise how fortunate they are just to be able to eat". The therapy group patients visited each other in hospital, wrote poems, and even had a meeting at the home of a dying member. Thus the groups countered the social alienation that often divides cancer patients from their well-meaning but anxious family and friends.

Involvement in the group may have allowed patients to mobilise their resources better, perhaps by complying more vigorously with medical treatment or by improving appetite and diet through reduced depression. Treated patients learnt about pain control and therefore may have been more able to maintain exercise and other routine activities. Neuroendocrine and immune systems may be a major link between emotional processes and cancer course.19,24 Future studies of the impact of psychosocial interventions on medical illness might profitably examine variables such as compliance, health habits, diet, and immune and neuroendocrine function.

This study was supported by grants from the National Cancer Institute (N01-CA-55313 [DHATT]), NIMH grant MH 16744, the American Cancer Research Fund, and the Alan and Lorraine Fischer Foundation. We thank the other therapists, Dr Irvin D. Yalom, Dr Regina Kris, and Susan Weisberg, Laina Kuppa for data analysis, Arnold M. Rey for research assistance, and Helen Abrahamson for manuscript preparation. We also thank the following doctors for critiques of earlier drafts: Helen Blau, Kenneth Bowren, Barrie Castellari, Hans Eysenck, Bernard Fox, James S. Goodwin, Jimmie Holland, Larry Kessler, Sandra M. Levy, Margaret Matson, Rudolph Moos, Gary R. Morrow, Helen Perfetti, Franke Stedelke, Aike Tellegen, Lydia Tomoshiba, and Irvin D. Yalom.

Correspondence should be addressed to D. S., Stanford University School of Medicine, Stanford, California 94305, USA.

REFERENCES


References continued at foot of next column.

GRANULOCYTE COLONY-STIMULATING FACTOR AND NEUTROPHIL RECOVERY AFTER HIGH-DOSE CHEMOTHERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION

W. P. SHERIDAN M. WOLF J. LUSK J. E. LAYTON L. SOUZA G. MORSYNY A. DODDS D. MAHER M. D. GREEN R. M. FOX

Department of Clinical Haematology and Medical Oncology, Royal Melbourne Hospital, Victoria; Melbourne Tumour Biology Branch, Ludwig Institute for Cancer Research, Melbourne; Department of Haematology--Oncology, Peter MacCallum Cancer Institute, Melbourne; Department of Haematology, St Vincent's Hospital, Sydney, Australia; and Argen Inc, Thousand Oaks, California, USA

Summary

Granulocyte colony-stimulating factor (G-CSF) was administered by continuous subcutaneous infusion to 15 patients with non-myeloid malignancies treated by high-dose chemotherapy and autologous bone marrow infusion. G-CSF was given at variable dosage based on neutrophil count. Sustained serum levels of G-CSF were achieved. Neutrophil recovery was accelerated in G-CSF treated patients compared with 18 historical controls and exceeded 0.5 x 10^9/L at a mean of 11 days after marrow infusion compared with 20 days for controls, a significant difference. This reduction led to significantly fewer days of parenteral antibiotic therapy, 11 versus 18 days in controls, and less isolation in reverse-barrier nursing, 10 versus 18 days.

Introduction

The dose of most anticancer agents is limited by myelosuppression. Drug dose is an important factor in tumour response and one approach to circumvent dose limits is haemopoietic rescue by autologous bone marrow.1 After such treatment there is a prolonged period of profound neutropenia during which patients are at risk of bacterial and fungal infection.6,7 Neutrophilic granulocyte production is stimulated by a haemopoietic growth factor, granulocyte colony-stimulating factor (G-CSF).8 The administration of G-CSF leads to a dose-dependent rise in peripheral blood neutrophils and reduces the period of neutropenia after standard-dose cytotoxic therapy.9-11 G-CSF 10 μg/kg per day or higher by continuous subcutaneous infusion abrogates the neutropenia seen after melphalan treatment.12 In primates G-CSF reduces the period of neutropenia after total body irradiation and autologous bone marrow infusion.13 Our objectives were to