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PRINCIPAL INVESTIGATOR: Doctor Dana H. Bovbjerg

CONTRACTING ORGANIZATION: Sloan-Kettering Institute for Cancer
Research
New York, New York 10021

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FOREWORD

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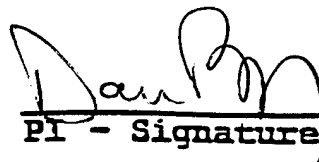
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5.0 INTRODUCTION

5.1 Subject, Purpose, and Scope of the Research

Neutropenia and the associated risk of infection in women receiving cytotoxic chemotherapy remains a significant clinical problem in the treatment of breast cancer. Dose intensification, which would increase the antineoplastic efficacy of standard chemotherapy treatments, is constrained by the increased risk of infection as the myelotoxic side effects become more severe. It is therefore important to consider factors that may contribute to the risk of infection in these patients. One such factor is suggested by accumulating evidence that psychological stress increases the risk of infection in otherwise healthy individuals. The ongoing research is the first to examine the effects of psychological stress on neutropenia and infectious disease in patients receiving chemotherapy. Greater understanding of the processes involved in the effects of psychological stress on neutropenia and infectious disease in these patients may lead to novel therapeutic approaches ranging from psychological interventions to pharmacologic manipulation of neuroendocrine influences on the immune system.

During this second year of the planned four-year study, our goals were to continue to recruit subjects and to conduct exploratory statistical analyses of some basic elements of the study, which can be appropriately addressed at this midway point of the research. As expected at this stage of our four-year prospective, longitudinal study, the currently available data do not provide sufficient statistical power for the specific aims to be fully addressed. On the other hand, data are sufficient to allow the preliminary investigation of one of the key issues directly relevant to the overall goal of the research; specifically, the possible relations between patients' psychological distress prior to chemotherapy and their subsequent experience of infectious disease. Fifty five subjects were recruited for this study.

5.2 The Background of Previous Work

The ongoing research, described below, investigates the hypothesis that psychological stress contributes to the increased risk of infectious disease in women receiving cytotoxic chemotherapy for breast cancer. This hypothesis is based upon three well established lines of research: 1) psychological stress (operationally defined either as negative events, or as negative emotional states) has been found to be associated with increased incidence and severity of a variety of infectious illnesses in otherwise healthy individuals facing the stresses of ordinary life [1,2]; 2) women diagnosed with breast cancer face the extraordinary stresses of life-threatening illness, disfiguring surgery, and the aversive side-effects of chemotherapy treatment

[3]; 3) concurrent with these psychological stresses, immune defenses against infectious disease are severely compromised during treatment as a result of myelotoxic side effects [4]. These three lines of previous work are reviewed briefly below. Considered together, this previous literature supports the view that the effect of psychological factors on infectious disease may be particularly potent in patients undergoing chemotherapy for breast cancer.

5.21 The effects of psychological stress on infectious disease: Two recent reviews of this literature have concluded that research evidence supports the view that psychological stress (defined in a number of ways) alters susceptibility to infectious disease, as well as influencing the severity and course of illness [1,2]. The studies summarized in these reviews indicate that: 1) during periods of psychological stress, individuals report more upper respiratory infections and are more likely to seek medical attention; 2) periods of psychological stress are associated with increased numbers of verified upper respiratory infections; 3) individuals with high levels of psychological stress have increased numbers of verified bacterial infections (e.g., streptococcal infections); 4) there is some evidence that psychological stress is associated with reactivation of latent viruses (e.g., herpes).

Perhaps the most convincing support for the hypothesis that psychological stress influences infectious disease comes from recent experimental studies in which men and women were deliberately exposed to live rhinoviruses [6-8]. Cohen and colleagues [6,8] found that the incidence of verified infection was higher in individuals reporting more perceived stress and negative affect prior to inoculation with live virus. As infectious symptoms are typically only seen in approximately two thirds of infected individuals, it was of interest that such symptoms (e.g., fever, runny nose) were found to be more common in individuals who experienced more major life events, the classic concept of Holmes and Rahe [9] over the year prior to experimental infection [8]. Similarly, we have found that experimentally infected individuals showing symptoms of infection, experienced more major life events (e.g., loss of job, promotion at work) in the year preceding the inoculation with live virus, compared to those without symptoms [7].

The effects of life events on infection are not limited to major stressors; changes in daily life events and psychological affect have also been found to be related to the onset of upper respiratory infections [10-12]. These studies have generally revealed a pattern of increased undesirable daily events and decreased desirable events four to five days before episodes of upper respiratory illness (defined by a constellation of daily self-reported symptoms) [10-13]. As symptoms of upper respiratory infection have been shown to develop two to three days after experimental infection [14], it is highly unlikely that these results are a consequence of the infectious disease itself.

The biological mechanisms linking psychological stress to increased incidence and severity of infectious disease are not yet well understood, but preclinical studies have revealed both afferent and efferent pathways linking the brain and the immune system [15]. Consistent with the possibility that altered immune defenses may mediate the relation between psychological stress and illness, studies of healthy individuals have repeatedly demonstrated that stress can affect both the number and activity of white blood cells [16,17].

5.22 Psychological distress associated with chemotherapy for breast cancer: In addition to the stresses posed by the diagnosis of cancer and disfiguring surgery [3], standard therapy for breast cancer increasingly includes repeated treatments with cytotoxic chemotherapy, which has a number of noxious side effects (e.g., nausea, hair loss). Heightened emotional distress in breast cancer patients during chemotherapy has been well documented both by our research group and others [18-21]. The highest levels of emotional distress have been repeatedly found to occur on the day of the first chemotherapy infusion [20,21].

5.23 Chemotherapy-induced neutropenia and risk of infection: Despite improvements in antibiotic treatments, infectious disease continues to be the leading cause of death for patients with neoplastic disease [4]. Patients with neoplastic disease, particularly those receiving cytotoxic chemotherapy treatment, such as those now in routine use for breast cancer, are at increased risk of developing a variety of infectious diseases associated with immune compromise [22]. These infections include both life-threatening episodes (e.g., systemic bacterial infection) and less serious episodes (e.g., recrudescence of herpes simplex virus) [22]. Although one would also expect significant increases in common upper respiratory illness, the ongoing study is the first to assess the full spectrum of infectious disease in women receiving chemotherapy for breast cancer.

Since the classic study by Bodey and colleagues [23], chemotherapy-induced granulocytopenia has become recognized as the single best predictor of infectious disease in cancer patients receiving cytotoxic chemotherapy, although deficits in cellular and humoral immunity are also likely to play a role [24]. Accumulating evidence indicates that the risk of infection is correlated with three indices of neutropenia derived from intensive assessment of the absolute neutrophil count (ANC): 1) the number of days with $ANC < 1000/mm^2$; 2) the lowest ANC (nadir level); and 3) the area defined by a plot of ANC across days where the ANC is $< 1000/mm^2$ [25]. This evidence has fueled considerable recent interest in treatment with granulocyte colony-stimulating factor (G-CSF) to speed recovery [25]. Although clinical trials suggest the potential clinical utility of G-CSF treatment, it should be

noted that such treatment shortens but does not eliminate chemotherapy-induced neutropenia [24].

Grounded in the previous research, reviewed above, the purpose of our ongoing research program is to investigate the effects of psychological stress on neutropenia and infectious disease in patients receiving standard cytotoxic chemotherapy treatment for breast cancer. More specifically, the present study tested the hypothesis that patients experiencing more emotional distress on the day of their first infusion of chemotherapy would have an increased incidence infectious disease during their course of their first three cycles of chemotherapy treatment.

6.0 BODY

6.10 Experimental Methods

6.11 Subjects

Fifty-six women scheduled to receive outpatient intravenous adjuvant infusions of chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil and/or adriamycin) for Stage I or II breast cancer, status post radical, modified radical, or segmental breast surgery were included in the study. All subjects in the study were patients who were treated with chemotherapy infusions on a three week cycle, which was accompanied by a standard regimen of I.V. antiemetic medications. The participants were consecutively recruited from an outpatient clinic to an ongoing research project; those with complete psychological and infection data were included in the present study. All subjects provided informed consent prior to their participation in the study and had to meet the following requirements: 1) at least 18 years of age; 2) not pregnant; 3) Karnofsky performance status greater than 70; 4) no previous chemotherapy treatment; 5) patient not scheduled to receive radiation or oral chemotherapy treatments during the course of their chemotherapy. Seventy-one percent of the patients had attended some college, 86% were employed outside the home, 64% were married, and 82% described themselves as white.

6.12 Procedures

Consecutive patients scheduled for chemotherapy, who were identified by their oncologists as meeting study criteria, were recruited for the study. Prior to their first treatment infusion, the study was explained and all participants provided written informed consent. As in our previous research [20,21], patients completed several study measures (described in detail below) in the clinic waiting area before treatment infusions. To reduce study burden, patients were also allowed to take several

measures home with them to complete at their convenience some time between infusions. For assessment of absolute neutrophil counts, blood samples were obtained by trained phlebotomists prior to treatment infusions. The measures included in the study are described in more detail below.

6.13 Measures

Demographic and Medical History Questionnaire: This questionnaire was developed by the investigators to assess standard demographic variables and to provide information on each patient's medical history. The self-reported information on medical history pertaining to their cancer and its treatment was confirmed by review of patients' medical charts.

Profile of Mood States (Short version): Prior to each chemotherapy infusion, patients completed the short version of the classic mood adjective checklist, the Profile of Mood States (POMS-SV) [26]. The POMS-SV contains 37 adjectives comprising six subscales (Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor-Activity, Fatigue-Inertia, and Confusion-Bewilderment), which are summed to provide a total mood disturbance (e.g., distress) score [26]. Patients were asked to respond accordingly to, How have you been feeling today, by rating each POMS-SV item on a zero to four scale (0 = not at all, 1 = a little, 2 = moderately, 3 = quite a lot, 4 = extremely) [26].

Impact of Event Scale Intrusion Subscale (IES-I): Prior to the first infusion, patients completed the intrusion subscale of the Impact of Event Scale (IES-I) [27] to measure intrusive thoughts about the upcoming chemotherapy infusion. The IES-I consists of seven sentences describing intrusive thinking, "over the past week including today." Each item was rated on a four point scale according to the following: 0 = not at all, 1 = rarely, 3 = sometimes, and 5 = often [27].

Visual Analog Scales (VAS): In the clinic, while awaiting chemotherapy infusions, participants completed VAS to assess the intensity of emotional upset and nausea, for "right now" as previously described [20,21]: Participants placed a slash across ten centimeter lines to indicate how they were feeling relative to anchor statements at the ends of each line. For emotional upset the VAS had anchors of "Not at all upset," and "As upset as I could be." For nausea the VAS had anchors of: "Not at all nauseated," and "As nauseated as I could be." Scores were obtained by measuring the distance in millimeters from the left end point of the line to the participants mark [20,21].

Infection Questionnaire: This brief questionnaire was designed by the investigators

to provide an indication of the prevalence of infectious disease between treatment infusions. Participants were asked to indicate the presence or absence of the following, since their previous chemotherapy infusion (a three week interval): Colds, fever, urinary tract infection, cold sores, or other infections. For the purposes of the present study, incidence of infectious disease was operationally defined by the self-reported number of colds, urinary tract infections, and other infections. Reports of fever and cold sores were excluded due to their potential lack of independence from reports of colds. As the incidence of infectious disease was relatively low and there was no significant difference ($p > 0.20$) in the incidence following the first, second, and third infusions, a combined infection score was created by summing the reported infections across the three cycles of chemotherapy.

Complete Blood Count (CBC): CBC with differential, performed by a clinical laboratory using laser light scatter and enzyme cytochemistry of coded samples, was assessed on the day samples were collected.

6.14 Statistical Analyses

Standard statistical analyses were performed using a statistical software package (SAS, Cary, SC). Preliminary analysis of the distribution of combined infection scores indicated a non-normal distribution ($p > 0.05$). Therefore, subsequent regression analyses in which the combined infection scores were the dependent variables were conducted with a Poisson distribution (SAS GENMOD procedure). To provide a more conservative approach to the results, we also treated infection as a dichotomous variable and examined relations to other study variables (e.g. psychological distress). That is, we compared those patients who reported experiencing one or more infectious diseases following the first three infusions of chemotherapy ($N = 28$) to those who did not experience any ($N = 28$).

6.20 Results

6.21 Relation between emotional distress prior to chemotherapy and subsequent incidence of infectious disease during treatment

Consistent with the study hypothesis, a regression analysis (Poisson) revealed that patients' total mood disturbance scores on the day of their first chemotherapy infusions predicted their subsequent experience of infectious disease across the first three cycles of treatment ($X^2 = 4.82, p \leq 0.03$). This relation is represented graphically in Figure 1, below. The more conservative statistical approach of comparing women who experienced one or more infectious diseases across the first three cycles of chemotherapy to women with none, also revealed a significant relation to their total

mood disturbance scores on the day of their first chemotherapy infusion [$F(1,55) = 3.88$, $p \leq 0.05$]. Interestingly, there were no significant differences between patients who did and did not have infectious diseases with regard to their intrusive thoughts or their acute distress at the time of the first infusion (p 's > 0.50).

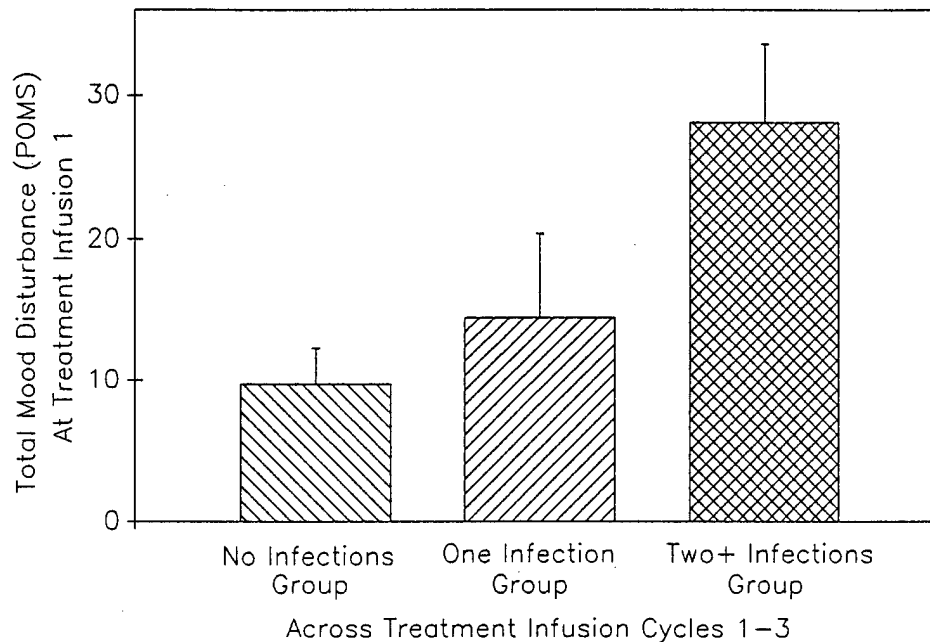


Figure 1

6.22 Could differences in demographic or medical variables have accounted for the relation between distress (POMS) and subsequent infectious disease?

In a correlational study such as this one, it is critical to consider the possibility that the relation between infectious disease and the patients' levels of emotional distress on the day of their first chemotherapy infusions could have been due to uncontrolled confounding variables. To address this possibility, we compared women who experienced one or more infectious diseases across the first three cycles of chemotherapy to women who experienced none. We found no significant differences between these two groups of women with regard to demographic variables, including: age, race, education, marital status, or employment status (p 's > 0.20). We also found no evidence to support the possibility that women with and without infectious diseases differed on relevant medical variables, including: the size of their tumors, the number of positive nodes, the tumor stage, the number of days since surgery, or the type of chemotherapy regimen (p 's > 0.20). We also found no support for the

possibility that group of women who developed infectious diseases may have been more likely to have received their first infusion during the cold/flu season ($p > 0.35$).

6.23 Could the relation between emotional distress (POMS) and subsequent infectious disease be due to differences in CBC counts prior to chemotherapy?

We examined the possibility that differences in CBC counts in blood samples collected a few minutes before the assessment of patients' distress (total mood disturbance, POMS) in the clinic prior to patients' first chemotherapy infusion may have been related to their subsequent development of infectious diseases. For these analyses, the women who subsequently experienced one or more infectious diseases across their first 3 cycles of chemotherapy were compared to those who experienced no infectious disease with regard to: white blood cell counts (WBC) absolute neutrophil counts (ANC), absolute lymphocyte counts (ALC), and absolute monocyte counts (AMC). As shown in Table 1, the women who subsequently developed infectious disease had significantly lower ANC prior to chemotherapy. ANC prior to chemotherapy, however, was not found to be significantly related to patients' levels of emotional distress (POMS) assessed at that time ($p > 0.20$). A logistic regression analysis entering both of these variables revealed significant, independent, main effects (with no interaction), indicating that emotional distress and absolute neutrophil counts on the day of patients' first chemotherapy infusion were independent predictors of the subsequent development of infectious disease (Table 2).

Relations Between Immune Measures and Infection

| | <u>No Infection</u> <u>Mean (SE)</u> | <u>Infection</u> <u>Mean (SE)</u> | <u>Statistics</u> |
|-----|-----------------------------------------|--------------------------------------|-------------------|
| WBC | 8.6 (0.9) | 7.0 (0.4) | $p \leq 0.08$ |
| ANC | 5.4 (0.7) | 3.6 (0.4) | $p \leq 0.03$ |
| ALC | 2.1 (0.2) | 2.3 (0.1) | $p \leq 0.40$ |
| AMC | 0.7 (0.1) | 0.5 (0.1) | $p \leq 0.29$ |

Table 1

Logistic Regression Analysis of Infection Incidence

| <u>Predictor</u> | <u>X²</u> | <u>Statistics</u> |
|------------------|----------------------|-------------------|
| ANC | 3.87 | $p \leq 0.05$ |
| POMS | 4.36 | $p \leq 0.04$ |

Table 2

6.30 Problems in accomplishing any of the tasks

We continue to have difficulty collecting CBC data on patients between treatment infusions. This information is no longer required as part of standard care and many patients willing to be in the study otherwise, are unwilling to provide the additional blood samples necessary. We have also had some difficulty getting patients to complete all study materials in a timely fashion (i.e., finish all questionnaires in clinic in the time available prior to treatment infusions). To address this issue, we have streamlined the questionnaires and focused the questionnaires in the clinic on time-dependent measures (e.g., distress right now) and allowed patients to take less time-critical measures home with them to complete at their convenience.

7. CONCLUSIONS

In this study we examined the relations between patients' levels of emotional distress, assessed as the total mood disturbance score (POMS), on the day of their first infusion of chemotherapy and their subsequent experience of infectious diseases during the first three cycles of chemotherapy. To our knowledge, the present study is the first to report that patients' levels of emotional distress prior to chemotherapy are related to their subsequent development of infectious diseases during chemotherapy.

These results should be interpreted with caution. Although consistent with a causal relation between distress and the subsequent experience of infectious disease, other explanations are also possible. As with all correlational studies, one must examine possible uncontrolled confounding variables that may account for the relations; in this case, the significant relation between emotional distress and infectious disease. It should be noted, however, that we found no support for alternative causal pathways, including the possibility of demographic or medical predictors of infection.

Given the self-report nature of the data collected in the present study, one must also be concerned that there could have been a possible reporting bias among the patients such that individuals who reported more distress also tended to report more infections. Two lines of evidence suggest that this explanation of the results is unlikely. First, if a reporting bias existed, one would expect that it would have been evident across all the psychological assessment instruments. However, only the POMS scores (distress on the day of infusion one) were significantly related to subsequent infection; patients' self reports of intrusive thoughts (IES) over the previous week and their acute levels of emotional distress (VAS) were not found to be related to infectious disease. Second, if reporting bias had a major impact on

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patients' reports of infection, how can one account for the significant relation between that data and the absolute neutrophil counts, assessed on the day of the first infusion?

The results of the present study, although preliminary, suggest the importance of continued research to examine the impact of psychological factors on infectious disease in patients receiving chemotherapy for breast cancer. It will be important to explore the impact of psychological variables on infection during the later phases of treatment and to examine possible biological mechanisms underlying the effects. The results to date also suggest the possible clinical benefit of psychosocial intervention to reduce emotional distress in patients on the day of their first chemotherapy infusion.

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