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Chemotherapy treatment for breast cancer can cause psychological distress on a daily basis and intense distress on treatment infusion days. Previous research raises the possibility that this stress may increase the risk of infectious disease. Our ongoing longitudinal study investigates this hypothesis. During this third year of the four year study, we recruited and studied 46 patients, and entered and verified their data, consistent with our Statement of Work. In addition, we analyzed results of one particularly relevant psychological variable, distress on treatment days (POMS) in a homogenous subset of patients. Results revealed that distress is highest prior to the first infusion, and suggest that effects on risk of infection may be most pronounced at that time.

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Overview

This annual report for Grant DAMD17-94-J-4141 covers research for the period June 8, 1996 - June 7, 1997. During that period, 46 breast cancer patients (22% minority women) were recruited for the research and underwent study assessments. Data from these assessments are continuing to be entered into a computerized database and verified. Combining these subjects with those recruited across the first two years of grant support (DAMD17-94-J-4141) 153 subjects have been recruited. The Statement of Work for this period (Year 3 of 4) indicates that 50 subjects should be recruited and studied, with data entered and verified. We are therefore four subjects short of the number specified for Year 3. We propose to make up for this shortfall by recruiting an additional four subjects during the next period of the research (i.e., during Year 4).

There have been no changes in the overall aims or design of the study. Consistent with the Statement of Work, we anticipate being able to satisfactorily address the three specific aims of the study, using data collected in accordance with the measures described in the original grant proposal, after we complete the planned recruitment of subjects (N=200) during Year 4 of funding.

In addition to recruiting, assessment, and data entry as specified by the Statement of Work for Year 3, we also examined one psychological variable particularly relevant to Specific Aim 2 in a selected, relatively homogenous, subset of participants. That is, we analyzed and subsequently published (see Appendix) the results of assessments of patients' distress levels conducted at each treatment infusion, for those patients receiving eight, three week, cycles of CMF (see below). To reduce patient burden of assessment conducted in the clinic while awaiting treatment infusions, distress levels were assessed with the short version of the Profile of Mood States developed by Shacham (1983), which we have demonstrated to have strong psychometric properties (DiLorenzo et al., submitted). These initial findings indicate that patients' stress levels are highest prior to their first treatment infusion, and suggest that the effects of stress associated with individual chemotherapy infusions on neutropenia and infectious disease in women receiving cytotoxic chemotherapy for breast cancer may be particularly critical after the first treatment infusion.

Introduction

The ongoing research 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 previous 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 (e.g., Cohen and Williamson, 1991; Peterson et al., 1991); 2) women diagnosed with breast cancer face the extraordinary stresses of life-threatening illness, disfiguring surgery, and the aversive side-effects of chemotherapy treatment (e.g., Jacobsen and Holland, 1991); 3) concurrent with these psychological stresses, immune defenses against infectious disease are severely compromised during treatment as a result of myelotoxic side effects (e.g., White, 1993). Considered together, this previous literature suggests that the effect of psychological factors on infectious disease may be particularly potent in patients undergoing chemotherapy for breast cancer.

Grounded in this previous research, the purpose of the ongoing research supported by DAMD17-94-J-4141 is to investigate the effects of psychological stress on neutropenia and infectious disease in patients receiving standard cytotoxic chemotherapy treatment for breast cancer. The aims of the study are as follows:

Specific Aim 1: To investigate the effects of major life events prior to treatment on neutropenia and infectious disease in women during chemotherapy treatment for breast cancer.

Specific Aim 2: To examine the effects of psychological distress associated with individual chemotherapy treatments on neutropenia and infectious disease in women receiving cytotoxic chemotherapy for breast cancer.

Specific Aim 3: To explore the relations between episodes of infectious disease and daily psychological stresses in women receiving cytotoxic chemotherapy for breast cancer.

As detailed in the original grant application, the study uses a longitudinal prospective design to concurrently assess psychological stress, neutropenia, and infection in 200 outpatients receiving a course of adjuvant chemotherapy treatment for early stage breast cancer. Briefly, psychological stresses are operationally defined as: 1) major life events over the year before treatment (baseline questionnaire data); 2) treatment-related psychological distress (questionnaire data collected prior to each treatment infusion); and, 3) daily events and emotional affect (questionnaire data collected daily by patients in their homes). Potential modifying (e.g., those that may affect levels of distress) variables, (e.g., family history of cancer, coping mechanisms) are assessed with questionnaires that patients are allowed to complete at their convenience at home. Neutropenia is assessed following clinical guidelines. Infectious disease is identified by data collected from: 1) patients' self-report daily questionnaires concerning symptoms of infectious disease and oral temperature; 2) telephone and personal interview data collected prior to treatment infusions; 3) review of clinical chart data.

Body

Introduction. The research project supported by DAMD17-94-J-4141 is designed to investigate the hypothesis that psychological stress contributes to the increased risk of infectious disease in women receiving myelotoxic chemotherapy for breast cancer. Psychological distress experienced by patients in the clinic prior to treatment infusions represents one possible source of such stress effects. During the third year of support, it was therefore of interest to investigate the intensity and pattern of self-reported distress assessed prior to each infusion across the course of a standard cytotoxic chemotherapy regimen for the adjuvant treatment of breast cancer. Although the literature includes clinical impressions of increasing distress across the course of chemotherapy (e.g., DeVita et al., 1993; Harris et al., 1996), empirical investigations examining this issue are scant. Our previously published studies (Sabbioni et al., 1992; DiLorenzo et al., 1995), which assessed patients at several points (e.g., beginning, middle, and end) during chemotherapy treatment using single item measures of psychological distress, suggested that distress might be particularly high in the clinic prior to a patient's first chemotherapy infusion.

Methods. As part of a larger investigation of psychobiological factors in patients receiving chemotherapy, consecutive patients scheduled for a standard cytotoxic chemotherapy regimen, CMF (cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2) i.v. q 21d) and identified as meeting study criteria, were recruited for the study. Eligibility criteria included: stage I or II breast cancer, post surgery, 18+ years of age, not pregnant, no previous history of chemotherapy treatment, received pretreatment chemotherapy teaching and uniform antiemetic treatments as part of routine clinical care. All participants provided written informed consent. All patients in the present study (N=33) completed the short version (Shacham, 1983) of the Profile of Mood States (POMS), a classic mood adjective checklist (McNair et al., 1971) in the clinic prior to each of 8 consecutive chemotherapy infusions beginning with their first. Few patients (mean = 1.8 patients per infusion) used anxiolytic or antiemetic medications (P.O.) prior to infusions. For purposes of comparison, a group (N=31) of healthy (self-report) female, hospital employees completed the short version of the POMS on a single occasion.

Results. Patients' total distress scores (POMS) were highest prior to the first infusion of chemotherapy and then declined ($p<.01$) to levels comparable to distress scores of hospital employees. Only at Infusion-1 were patient distress levels significantly higher than employee levels ($p < .05$). Patients' distress levels were not predicted by: age, ethnic group, marital status, whether they were scheduled for another treatment modality (e.g., radiation), or by the number of positive nodes ($p > .05$), but were related to tumor size and cancer stage ($p < .05$). None of these factors affected the pattern of reduced distress following Infusion-1.

Conclusions

The results presented above, confirm and extend previous reports (Sabbioni et al., 1992; DiLorenzo et al., 1995) that patients' distress levels are higher prior to their first scheduled chemotherapy infusion than at any other time during their chemotherapy regimen. With regard to the specific aims of the ongoing research supported by DAMD17-94-J-4141, these initial results suggest that the impact of psychological distress associated with chemotherapy infusion days on patients' risks of infectious disease is likely to be most pronounced in the early phase of adjuvant treatment for breast cancer. These results are thus consistent with our preliminary analyses of data indicating a positive relationship between distress levels (POMS) on the day of the first infusion of chemotherapy and subsequent risk of infectious disease (see Progress Report, 1996). This relationship between preinfusion distress and risk of infectious disease (Specific Aim 2) will be examined more comprehensively upon completion of the data collection in Year 4 of the study, along with the other two major aims.

References

Chanock S. (1993). Evolving risk factors for infectious complications of cancer therapy. Hemat Oncol Clin N Amer; 7:771-93.

Cohen S, Williamson GM. (1991). Stress and infectious disease in humans. Psychological Bulletin; 109:5-24.

DeVita VT, Hellman S, Rosenberg SA. (1993). Principles and Practice of Oncology. Philadelphia: Lipppincott.

DiLorenzo TA, Jacobsen PB, Bovbjerg DH, Cheng H, Hudis C, Sklarin N. (1995). Sources of anticipatory emotional distress in women receiving chemotherapy for breast cancer. Annals of Oncology; 6:705-711.

Harris JR, Lippman ME, Morrow M, Hellman S. (1996). Diseases of the Breast. Philadelphia: Lipppincott.

Jacobsen PB, Holland JC. (1991). The stress of cancer: Psychological response to diagnosis and treatment. In, Cooper CL, Watson M (eds) Cancer and Stress: Psychological, Biological, and Coping Studies. Chicester, U.K.: Wiley, pp 147-169.

McNair DM, Lorr M, Droppelman L. (1971). Manual: Profile of Mood States. San Diego: EDITS/Educational and Industrial Testing Service Inc.

Montgomery GH, McClary KA, Bovbjerg DH. (1996). Adjuvant therapy for breast cancer and psychological distress. Annals of Oncology; 7:977-978.

Peterson PK, Chao CC, Molitor T, Murtaugh M, Strgar F, Sharp BM. (1991). Stress and pathogenesis of infectious disease. Rev Infectious Dis; 13:710-20.

Sabbioni ME, Bovbjerg DH, Jacobsen PB, Manne SL, Redd WH. (1992). Treatment related psychological distress during adjuvant chemotherapy as a conditioned response. Annals of Oncology; 3:393-398.

Shacham N. (1983). A shortened version of the profile of mood states. J. Personal. Assess; 47:305-306.

White MH. (1993). Prevention of infection in patients with neoplastic disease: use of a historical model for developmental strategies. Clin Infectious Dis; 17:S355-58.

Appendix A: Montgomery GH, McClary KA, Bovbjerg DH. (1996). Adjuvant therapy for breast cancer and psychological distress. Annals of Oncology; 7:977-978.

Annals of Oncology 7: 977–979, 1996.

Letters to the editor

The Rosai–Dorfman Syndrome in a 17-year-old woman with transformation into high-grade lymphoma. A rare case presentation

The Rosai–Dorfman Syndrome, better known as sinus histiocytosis with massive lymphadenopathy (SHML), is a rare benign disease of unknown etiology. Persistent painless lymphadenopathy due to expansion of sinuses infiltrated with benign histiocytes and plasma cells is the characteristic feature of SHML [1]. Here, we present a rare case of Rosai–Dorfman Syndrome with transformation into high-grade lymphoma.

Case history

A 17-year-old white woman was admitted to the Cancer Center in Krakow. She had been referred by the local hospital where she was treated with antibiotics due to enlargement of cervical lymph nodes associated with fever. On admission, the patient presented massive cervical, bilateral lymphadenopathy, fever and general malaise. Chest X-ray and abdomen CT scan revealed no pathological changes. Eosinophilia was reported in the bone marrow aspirate. A cervical lymph node was excised and a histopathological diagnosis of Rosai–Dorfman Syndrome was established. An elevated erythrocyte sedimentation rate, leukocytosis, anemia and hypergammaglobulinemia were present. Flow cytometry revealed an immune dysfunction (decreased T-helper lymphocyte subpopulation). The result of an anti-HIV antibody test was negative. Cytogenetic studies were performed on bone marrow cells obtained from a sternal biopsy. All 35 analysed metaphases were normal, with karyotype 46, XX.

No treatment option was chosen. The patient was followed every 3 months and after 5 years of observation a rapid progression of the disease was documented. An excised axillary lymph node revealed a high-grade lymphoma. VACOP-B chemotherapy was administered and resulted in a clinical partial remission. Cervical lymph nodes and pharynx were treated with radiotherapy. A total dose of 5000 cGy in 25 fractions was given. The patient was in remission for 15 months.

The second-line chemotherapy with the ESA regimen was used due to recurrence. The patient has been in remission for 3 months with moderate doses of prednisone (15 mg) as maintenance therapy.

Discussion

The Rosai–Dorfman Syndrome is a very rare condition with a benign course. Spontaneous remissions have been observed, although severe immune dysfunction has been found to be associated with SHML [2]. In a literature review of 462 cases of this disease, the development of lymphomas was observed in 6 patients [3].

According to our observation and information from the literature [4], cases with transformation into non-Hodgkin's high-grade lymphoma require intensive treatment. It is possible that a complete remission cannot be achieved because of heterogenity of lymph node lesions (the co-existence of lymphoma and SHML cells) and observed remissions are associated with lymphoma component [5].

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References

1. Thomson ER, Newman P, Dunstan S, Coull H. The Rosai Dorfman Syndrome in 50-year-old male. Br J Oral Maxillofac Surg 1989; 27(1): 39–45.
2. Komp DM. The treatment of sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman disease). Semin Diagn Pathol 1990; 7(1): 83–6.
3. Koduru RK, Susin M, Kolitz JE et al. Morphological, ultrastructural and genetic characterization of an unusual T-cell lymphoma in a patient with sinus histiocytosis with massive lymphadenopathy. Am J Hematol 1995; 48: 192–200.
4. Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy: A pseudolymphomatous benign disorder. Analysis of 34 cases. Cancer 1972; 30: 1174–88.
5. Foucar E, Rosai J, Dorfman RF. Sinus histiocytosis with massive lymphadenopathy (Rosai Dorfman disease). Semin Diagn Pathol 1990; 7: 19–73.

Adjuvant therapy for breast cancer and psychological distress

Despite continuing improvements in the clinical management of aversive side-effects of chemotherapy treatment for cancer, there remains a widespread perception among health care professionals that patients experience increasing levels of emotional distress across the protracted course of infusions required for therapy [1, 2]. There is little empirical evidence to support this clinical impression, however.

We assessed emotional distress in 33 women receiving a complete course of adjuvant systemic chemotherapy, which consisted of a classic regimen of eight cycles of a standard combination of cytoxic agents, CMF (cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and 5-fluorouracil (600 mg/m^2)) i.v. q 21d. Eligibility criteria included: stage I or II breast cancer; post surgery (e.g., mastectomy); 18+ years old; not pregnant; received pretreatment chemotherapy teaching and uniform antiemetic treatments (i.v.), as part of routine clinical care. Few patients (mean = 1.8 patients per infusion) used anxiolytic or antiemetic medications (p.o.) prior to infusions. Emotional distress on the day of each treatment infusion was assessed with a short version of the

Profile of Mood States (POMS), a classic classic mood adjective checklist [3], which patients completed in the waiting room before each infusion. Healthy (self-report), female, hospital employees ($n = 31$) completed the POMS on a single occasion.

Patients' total distress scores (POMS) were highest prior to the first infusion of chemotherapy and then declined ($P < 0.01$) to levels comparable to distress scores of hospital employees (Figure 1). Only at Infusion-1 were patient distress levels significantly higher than employee levels ($P < 0.05$). Patients' distress levels were not predicted by: age, ethnic group, marital status, whether they were scheduled for another treatment modality (e.g., radiation), or by the number of positive nodes ($P > 0.05$), but were related to tumor size and cancer stage ($P < 0.05$). None of these factors affected the pattern of reduced distress following Infusion-1.

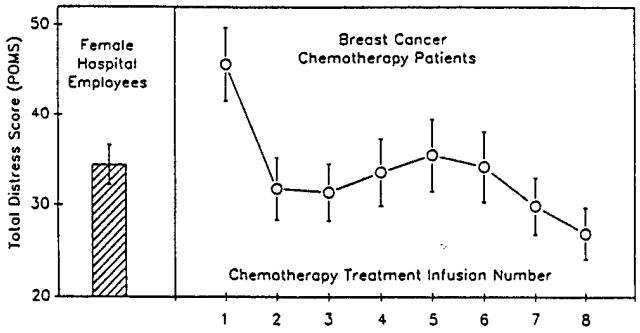

Figure 1. Changes in psychological distress scores (mean + SE) across a regimen of outpatient chemotherapy (CMF, i.v.) for breast cancer.

These results, based on patients receiving CMF, are consistent with our previous studies using single-item measures of distress [4, 5] and provide no support for the widespread view that patients typically develop more distress as they go through repeated cycles of chemotherapy treatment for cancer. To our knowledge all the available data indicate that patients' distress levels are higher prior to treatment than at any other time during chemotherapy. The sources of this pretreatment distress have yet to be determined, but may include negative expectations of side-effects, loss of control, and/or fear related to this novel experience.

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References

1. DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles & Practice of Oncology. Philadelphia: Lippincott 1993.
2. Harris JR, Lippman ME, Morrow M, Hellman S. Diseases of the Breast. Philadelphia: Lippincott 1996.
3. McNair DM, Lorr M, Droppelman L. Manual: Profile of Mood States. San Diego: EDITS/Educational and Industrial Testing Service Inc. 1971.
4. Sabbioni ME, Bovbjerg DH, Jacobsen PB et al. Treatment related psychological distress during adjuvant chemotherapy as a conditioned response. Ann Oncol 1992; 3: 393–8.
5. DiLorenzo TA, Jacobsen PB, Bovbjerg DH et al. Sources of anticipatory emotional distress in women receiving chemotherapy for breast cancer. Ann Oncol 1995; 6: 705–11.

Rapid intravenous premedication with dexamethasone prevents hypersensitivity reactions to paclitaxel

Introduction

Paclitaxel is a highly active new drug in the treatment of various types of tumors; however, in early phase I testing [1], the speed of clinical development has been partially hampered by hypersensitivity reactions. In the subsequent clinical trials paclitaxel was administered by continuous infusion over 24 hours and a premedication regimen consisting of oral corticosteroids administered 12 and 6 hours before treatment, orphenadrine and cimetidine, was instituted; this premedication was successful in reducing the incidence of severe hypersensitivity reactions to less than 5% [2].

Moreover, the 3-hour infusion has also proven safe, but the timing of premedication is still rather cumbersome for routine use in the outpatient setting [3].

In the current report we compare the use of a rapid intravenous premedication with dexamethasone with standard prolonged oral premedication in patients treated with paclitaxel given over 3 hours.

Patients and methods

Patients with advanced cancer who had progressed after standard chemotherapy were eligible for paclitaxel.

All patients had histologically confirmed diagnoses of cancer; other eligibility criteria included: age ≤ 70 years, an ECOG performance status ≤ 2, normal bone marrow, liver and renal functions.

Standard premedication consisted of oral prednisone 125 mg 12 and 6 hours prior to paclitaxel infusion.

The intravenous premedication was approved by the local ethical committee and the patients gave their informed consent before treatment. Intravenous premedication consisted of dexamethasone 20 mg administered by intravenous bolus immediately before the start of paclitaxel.

All of the patients were also premedicated with intramuscular orphenadrine 50 mg plus intravenous cimetidine 300 mg one hour before start of treatment The calculated dose of paclitaxel was diluted in 500 ml of saline and administered over 3 hours. Only glass containers and polyethylene-lined tubing were used for drug delivery. In-line filtration of the prepared solution during paclitaxel infusion using cellulose acetate filters of 0.22 μm pore size was performed.

During paclitaxel administration blood pressure, heart rate and respiratory frequency were recorded every 20 minutes.

Severe hypersensitivity reactions were graded, according to WHO [3], as reactions with one or more of the following: angioedema, hypotension (SBP < 80 mmHg), respiratory distress requiring bronchodilators or generalized urticaria.

If any of these symptoms occurred, paclitaxel infusion was stopped and treatment for anaphylaxis with additional corticosteroids, antihistamines and bronchodilators instituted.

If mild or moderate symptoms of hypersensitivity occurred, the infusion was temporarily discontinued and 250 ml of saline were administrated before paclitaxel was started again.