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What is This?
Levels of Fatigue Compared to Levels of Cytokines and Hemoglobin during Pelvic Radiotherapy: A Pilot Study

Karin Ahlberg, RN, MSc
Tor Ekman, MD, PhD
Fannie Gaston-Johansson, RN, PhD

Cancer-related fatigue (CRF) is a prevalent and distressing symptom experienced by patients during cancer therapy. One proposed mechanism for the development of fatigue is the increased secretion of proinflammatory cytokines and/or the development of anemia. The major purpose of this pilot study was to investigate the levels of fatigue and cytokines during radiation therapy and determine whether there was a correlation between the two. A secondary purpose was to explore the relationships among hemoglobin values, cytokines, and fatigue. Participants included 15 women diagnosed with uterine cancer, who received curative external radiation therapy. Fatigue was assessed by a self-report instrument (Multidimensional Fatigue Inventory [MFI-20]) and hemoglobin and cytokines (IL-1, IL-6, and TNF-α) were measured before, during, and after radiotherapy. The degree of fatigue increased during radiotherapy without a significant change in IL-1, IL-6, or TNF-α levels. There was no significant correlation between changes in general fatigue and the changes in IL-1 and TNF-α. There was a significant negative correlation between the change in IL-6 and general fatigue. The hemoglobin levels did decrease significantly during radiotherapy, but there was no significant correlation between general fatigue and hemoglobin after 3 weeks of therapy or after the completion of therapy. In conclusion, pelvic radiotherapy in women with uterine cancer is associated with increased fatigue. There were no significant relationships between anemia or cytokine levels and fatigue. The pathogenesis of fatigue during radiation therapy remains to be elucidated.

Key words: cancer, cytokine, fatigue, hemoglobin, radiotherapy, correlation

Patients treated for gynecologic cancer experience significant problems, such as side effects from the treatment, changes in body image and function, and major disruptions in life situations. The different treatment modalities of surgery, chemotherapy, and external and internal radiation therapy cause different acute side effects.

Fatigue is a subjectively experienced symptom and can be described in terms of perceived energy, mental capacity, and psychological status. Cancer-related fatigue (CRF) may be defined as “an unusual, persistent,
subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning” (Mock and others 2000). CRF is one of the most frequently reported symptoms in patients with cancer as well as in connection with anticancer therapy (Curt 2000; Ahlberg and others 2003) and is a major obstacle to normal functioning and to a good quality of life in these patients (Morrow and others 2002).

Many patients experience fatigue during and immediately after radiotherapy (Smets and others 1998). The reported incidence of fatigue when a patient is treated with external and/or intracavity radiation therapy varies between 65% and 100%, and in some cases it may persist for months or years after treatment ends (Monga and others 1997; Smets and others 1998; Ahlberg and others 2003). Fatigue usually develops during the 1st week of treatment and then diminishes 2 to 4 weeks after completed treatment. In several studies, patients have identified fatigue as the worst side effect during the last week of treatment (Peck and Boland 1977; Haylock and Hart 1979; King and others 1985; Smets and others 1998), particularly in the afternoons (King and others 1985). The level of fatigue slowly decreases to pretreatment levels by 3 months after treatment (Irvine and others 1998; Schwartz and others 2000).

Researchers have proposed that 1 possible explanation for the development of fatigue in cancer patients is the increased secretion of proinflammatory cytokines in response to both the disease itself and the treatment (Greenberg and others 1993; Kurzrock 2001). Proinflammatory cytokines—interleukins, interferon, or tumor necrosis factor—are proteins that mediate cell-to-cell communication. Herskind and others (1998) reported that they are released in greater amounts in patients with cancer as part of the host response to the tumor, in response to tissue damage, or due to depletion of immune-cell subsets associated with treatment for the disease. Fatigue is also one of the most common symptoms of anemia, with the level of fatigue influenced by the degree of anemia (Yellen and others 1997). CRF due to anemia has been studied frequently in connection with chemotherapy but not particularly during and after radiotherapy.

The present study investigated whether there is a relationship between the levels of fatigue and serum levels of interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF-α) over time in patients during pelvic radiotherapy for uterine cancer. This study also explored the relationship between hemoglobin and IL-1, IL-6, TNF-α, and fatigue.

**Materials and Methods**

**Study Population**

The pilot study population consisted of women diagnosed with uterine cancer who received external radiation therapy (46 Gy, 2 Gy/fraction, 4 days/week) after hysterectomy. Other inclusion criteria were that the patients gave informed consent, had the ability to understand, speak, and read Swedish, and understood the purpose of the study as well as the testing procedures involved. The exclusion criteria were evidence of dementia or a known history of psychiatric disorder.

Due to the high cost of performing cytokine measures, we decided to explore the relationships among the variables of interest after 15 patients had been enrolled. With a sample size of \( N = 15 \) and a correlation coefficient of \( r = -0.54 \), tests were conducted with a power of 63%. To achieve 80% power with a correlation coefficient of \( r = -0.54 \), a sample size of \( N = 22 \) would be needed.

**Study Variables and Instruments**

**Fatigue**

Fatigue was measured with a Swedish version (Fürst and Åhsberg 2001) of the Multidimensional Fatigue Inventory (MFI-20) (Smets and others 1995). The instrument consists of 20 items and covers 5 dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fa-
tigue. The MFI-20 has been used in several studies of cancer patients and has demonstrated high reliability and validity in patients receiving radiotherapy (Smets and others 1995). The Swedish version of the MFI-20 has shown good internal consistency (0.75–0.94) (Furst and Åhsberg 2001).

Cytokines (IL-1, IL-6, TNF-α)

Peripheral venous blood samples were drawn into sterile endotoxin-free blood collection tubes. The tubes were centrifuged for 20 min at 3000 rpm at 4 °C. The plasma samples were frozen at –70 °C until the analyses were performed. Plasma levels of IL-1 and TNF-α were determined by an ELISA procedure (Medgenix, Fleurs, Belgium) using recombinant proteins to construct a standard curve. Plasma levels of IL-6 were analyzed using a bioassay procedure, using cell line B13.29; subclone B9, is known to be dependent on IL-6 for growth.

Hemoglobin

Hemoglobin was measured according to standard procedures at the laboratory at Sahlgrenska University Hospital.

Procedure

The study took place at the Department of Oncology, Sahlgrenska University Hospital, where patients from both the city of Gothenburg and the western region (population 1.5 million) are referred for radiotherapy. The project leader and the research nurses consecutively identified potential participants who met the inclusion criteria through the hospital’s clinical database. All potential participants received verbal and written information and gave verbal consent. Fifteen patients were included in this pilot study. The data were collected before start of radiotherapy, after 30 Gy (+3 weeks) and after completed treatment with 46 Gy (+5 to 6 weeks). Finally, cytokines were measured 1 week after the completed radiotherapy.

Patients completed the MFI-20 at baseline (i.e., before radiotherapy treatment began) in a private room at the hospital. They completed the questionnaire after 30 Gy and 46 Gy when they were visiting the radiation unit. Blood samples to be used for analysis of cytokine and hemoglobin levels were taken the same day as the fatigue measurements in connection with the participants’ visits to the hospital. There were no missing data. Demographic and clinical data (age, cancer stage) were extracted from the patients’ records. All data were collected during 2002.

Statistical Methods

Mean, standard deviation (SD), median, and range were calculated for descriptive purposes. All correlations were analyzed with Pitman’s nonparametric permutation test. In addition, Pearson’s correlation coefficient was calculated for descriptive purposes. For comparison over time, Fisher’s nonparametric permutation test for matched pairs was used. All tests were 2-tailed and conducted at a 5% significance level.

Ethics

The study was done in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, revised in 1983. Ethical considerations in this study concerned individual autonomy, informed consent, and the risk of causing emotional injury through the questionnaire. The study protocol was approved by the Ethical Committee of Sahlgrenska University Hospital, and all the patients gave informed, verbal consent before inclusion.

Results

The median age of the 15 participants was 63 (range 50–81). The majority of the patients, 86%, had stage I disease, 7% had stage II, and another 7% had stage III (Creasman and others 2001). The general fatigue score increased significantly during radiotherapy, with medians of 8 (range 4-20) at baseline, 12 (range 5-20) after 3 weeks of treatment ($P < 0.001$), and 13 (range 4-20) after completed therapy ($P < 0.001$) (Table 1).

Cytokines and Fatigue

The levels of IL-1 remained below the detection limit during the entire study period. TNF-α increased above the detection limit after 3 weeks in 5 out of 15 patients ($P = 0.94$) and in 4 out of 15 patients after
completed therapy ($P = 0.88$). It increased in only 1 patient at both measure points. The levels of IL-6 increased after 3 weeks of treatment in 7 patients and decreased in 8 patients ($P = 0.52$). After completed therapy, the levels for 8 patients increased and for 7 decreased ($P = 0.72$). For 9 patients, the level of IL-6 was higher than the normal value (> 85 pg/mL) from the beginning. Two of these patients had an increase in IL-6 after 3 weeks of therapy and 6 after completed therapy (Figures 1 and 2). There was a significant negative correlation between the change from baseline to 3 weeks of treatment ($r = –0.65, P = 0.006$) and to end of treatment ($r = –0.54, P = 0.04$) in IL-6 and general fatigue. No significant correlation was found between fatigue and TNF-α in the changes from baseline to 3 weeks of treatment or to end of treatment (Table 1).

Hemoglobin and Fatigue

Hemoglobin (normal range 116–149 g/l) decreased significantly ($P < 0.001$) from a median of 137 g/l (range 128–147) at baseline to 131 g/l (range 118–144) after 3 weeks of therapy and 129 g/l (range 114–144) after completed radiotherapy. There was no significant correlation between changes in general fatigue and hemoglobin from baseline to 3 weeks of therapy ($r = 0.04, P = 0.79$) or to completed therapy ($r = –0.18, P = 0.23$) (Table 1).

Discussion

This study showed that the degree of fatigue increased during radiotherapy without a significant change in serum levels of IL-1, IL-6, or TNF-α. There was no significant correlation between changes in general fatigue and the changes in IL-1 and TNF-alpha. There was a significant negative correlation between the change in serum IL-6 and general fatigue. There was no significant correlation between general fatigue and hemoglobin.

Fatigue and Radiotherapy

Several investigators have demonstrated that fatigue increases during radiation therapy. Monga and others (1999) measured fatigue with the Piper Fatigue Scale before, at the midpoint of, and after completion of external radiotherapy in 36 men with prostate cancer. Mean fatigue score increased from 2.60 to 3.49 to 3.97; 3 patients scored 6 or higher (a score of 6 or higher indicates a significant level of fatigue) at the beginning of radiotherapy; and 9 patients scored 6 or higher at the completion of radiotherapy. In the same study, corroborating our findings, no significant changes in hematocrit levels were found. Janda and others (2000) also reported a significant increase in fatigue (measured by a quality-of-life instrument from the European Organisation for Research and Treatment of Cancer [EORTC], QLQ-C30) in men treated with external radiation for prostate cancer.

The authors have not been able to find comparable reports investigating the same population as in the present study. However, the studies presented above support the finding in the present study that abdominal radiation increases the level of fatigue. The mechanisms of radiation-induced fatigue are not understood, but investigators have proposed them to be anemia, reduced neuromuscular efficiency (Monga and others 1997), or an inflammatory response (Kurzrock 2001).

Fatigue and Cytokines

In noncancer patients, fatigue is a common symptom accompanying acute and chronic inflammatory illness and infection. High levels of TNF-α, IL-1, and IL-6 have also been described in a variety of cancers and may contribute to symptoms such as fever, weight loss, sweats, and anemia, as well as to fatigue (Kurzrock 2001). Increased levels of cytokines could contribute to the development of fatigue through effects on the endocrine system and neurotransmitters as, for example, in chronic fatigue syndrome (Buchwald and others 1997; Moss and others 1999). Furthermore, IL-6 has been postulated to be involved in sleep onset (Redwine and others 2000) and sleep deprivation (Vgontzas and others 2000). Blocking the production of TNF-α, thus decreasing disease activity in rheumatoid arthritis, has also been associated with a decrease in fatigue, supporting indirectly the hypothesis that TNF-α could mediate the development of fatigue (Elliott and others 1994). A release of inflammatory mediators may contribute to fatigue in connection with tumor diseases (Yellen and others 1997). Accordingly, it has been demonstrated in animal models of total body or localized irradiation that serum levels of IL-1, IL-6, and TNF-α increase. In hu-
Table 1. Fatigue Scores and Cytokine and Hemoglobin Levels at Baseline, after 3 Weeks of Radiotherapy (+30 Gy) and after Completed Radiotherapy (+46 Gy) 
(N = 15)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>+30 Gy</th>
<th>+46 Gy</th>
<th>Change from Baseline to +30 Gy</th>
<th>Change from Baseline to +46 Gy</th>
<th>Correlation, change from baseline to +30 Gy, with fatigue</th>
<th>Correlation, change from baseline to +46 Gy, with fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>M (SD)</td>
<td>P value</td>
<td>P value</td>
<td>P value</td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>md (range)</td>
<td>md (range)</td>
<td>md (range)</td>
<td></td>
<td></td>
<td>Pearson r</td>
<td>Pearson r</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.9 (4.7)</td>
<td>12.1 (4.6)</td>
<td>13.3 (5.4)</td>
<td>3.2 (2.7) &lt; 0.001</td>
<td>4.3 (3.7) &lt; 0.001</td>
<td>0.79</td>
<td>0.23</td>
</tr>
<tr>
<td>TNF-α</td>
<td>2.9 (8.1)</td>
<td>3.3 (5.0)</td>
<td>2.4 (4.3)</td>
<td>0.4 (10.2) 0.94</td>
<td>0.5 (6.8) 0.88</td>
<td>0.51</td>
<td>0.50</td>
</tr>
<tr>
<td>IL-1</td>
<td>0 (0-31)</td>
<td>0 (0-14)</td>
<td>0 (0-12)</td>
<td>0 (-31-14) 0.94</td>
<td>0 (-19-10)</td>
<td>0.51</td>
<td>0.50</td>
</tr>
<tr>
<td>IL-6</td>
<td>80.3 (24.3)</td>
<td>75.1 (22.8)</td>
<td>78.7 (21.6)</td>
<td>-5.2 (30.4) 0.52</td>
<td>-1.6 (16.4) 0.72</td>
<td>0.006</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>137 (6)</td>
<td>131 (7)</td>
<td>130 (9)</td>
<td>-6.9 (4.5) &lt; 0.001</td>
<td>-7.7 (7.2) &lt; 0.001</td>
<td>0.79</td>
<td>0.23</td>
</tr>
</tbody>
</table>

* a. P value cannot be estimated.
mans, radiation therapy has been shown to increase serum levels of proinflammatory cytokines such as IL–1 (Kurzrock 2001) or IL–6, at least among those patients who later developed radiation pneumonitis (Chen and others 2001). As cancer therapy can elicit fatigue or increase preexisting fatigue, cytokine levels during abdominal radiation therapy were considered to be of interest in the present study. The negative correlation between changes in serum IL–6 and fatigue was unexpected. A larger sample is needed to verify this relationship in this population of patients.

There is some evidence that psychological stress may suppress or enhance immune functions in humans and experimental animals, depending on the nature of the stressor and the immune variables under consideration. A study by Steptoe and colleagues (2001) indicates that inflammatory cytokines respond to acute mental stress in humans with delayed increases and suggests that individual differences in cytokine responses are associated with sympathetic reactivity. Maes and colleagues (1998) investigated the possibility that psychological stress may affect the production of proinflammatory and immunoregulatory cytokines in a study involving 38 medical students. Findings suggest that, in humans, changes in the production of IL–6, among other cytokines, are a part of the homeostatic responses to psychological stress and that stress-induced anxiety is related to a T-helper-1-like response. Thus, although a very preliminary finding, the negative correlation between general fatigue and IL–6 could form a basis for a preliminary hypothesis that stress and fatigue are affecting, or being affected by, different reactions in the immune system.

Fatigue and Hemoglobin

Cytotoxic therapy and radiation therapy could contribute to the development of anemia through a direct effect on hematopoietic precursors or through inducing an inflammatory response, which could suppress erythropoiesis. In the present study, pelvic irradiation was accompanied by a small but significant reduction in hemoglobin. The undetectable levels of IL–1 throughout the study period, the absence of a correlation between fatigue and TNF–α, and the negative correlation between IL–6 and fatigue seem to contradict the hypothesis that an inflammatory reaction was the cause of this reduction in hemoglobin. A natural explanation of the increase in fatigue, as noted in the present study, could be the reduction in hemoglobin levels, although no correlation was found between changes in hemoglobin and changes in fatigue. It would be of interest to investigate this preliminary finding further in a larger sample. Accordingly, in the most cited study investigating the effect of erythropoietin therapy on fatigue, the placebo group had constant hemoglobin levels during the study period but at the same time experienced an increase in fatigue (Littlewood and others 2001). In another randomized and double-blind study...
on hematologic malignancies, patients in the active arm had a lesser transfusion requirement and a higher percentage of increase in hemoglobin (more than 2 g/dl as well as less pronounced hemoglobin nadirs) than the control group without any significant difference between the groups in the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) subscale scores (Österborg and others 2002). In other words, it appears that erythropoietin therapy increases hemoglobin and reduces fatigue when compared to the use of placebo, but an increase in fatigue during chemotherapy is not explained by a worsening of anemia. Thus, anemia cannot be singled out as the only factor responsible for fatigue during chemotherapy or radiation therapy.

**Conclusion**

In this pilot study, cytokine liberation did not correlate with the increased experience of fatigue in women with uterine cancer during or after pelvic radiotherapy. The pathogenesis for the symptom of fatigue remains to be elucidated.

**References**


