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ORIGINAL ARTICLE

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# Impact of chemotherapy-induced neutropenia on quality of life: a prospective pilot investigation

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**Abstract** *Purpose:* In this exploratory, prospective study evaluated quality of life (QoL) changes in patients with diverse cancers during the first cycle of myelosuppressive chemotherapy. *Patients and methods:* Of 80 patients enrolled, 71 were observed during one of five chemotherapy regimens: docetaxel; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); carboplatin-paclitaxel; carboplatin-docetaxel; and carboplatin-gemcitabine. Complete blood counts were taken weekly. QoL and symptom burden measures were administered at baseline and throughout the cycle, and included SF-36, Cancer Care Monitor (CCM), Hospital Anxiety and Depression Scale (HADS), and Psychosocial Adjustment to Illness Scale (PAIS). Using generalized estimating equations, we modeled the change in each measure from baseline to the end of each week using the following covariates: baseline QoL measure, baseline SF-36 Physical and Mental Health Summary scores, sex, age, cycle week, grade 4 neutropenia any time in the past 7 days (yes/no), and the interaction of the latter two covariates. *Results:* Of the 71 patients observed, 33 developed grade 4 neutropenia during the first 2 weeks. Changes from baseline in SF-36 Bodily Pain, HADS Anxiety, and PAIS Social Environment scores were significantly less favorable ($P<0.05$) when patients experienced grade 4 neutropenia any time in the past 7 days compared to when they did not (grade 0–3). A similar, but non-significant, trend was also observed for 12 other QoL measures. *Conclusion:* QoL may be adversely affected up to 7 days after patients experience grade 4 (versus grade 0–3) neutropenia. Such findings need to be examined further in studies with adequate statistical power to test a priori hypotheses regarding specific QoL measures.

**Keywords** Chemotherapy-induced neutropenia · Quality of life

## Introduction

Neutropenia frequently occurs with myelosuppressive chemotherapy [1]. This condition may put patients at risk for infections and hospitalizations as well as for decreased survival because of chemotherapy dose reductions or delays [2–5]. Five grades of neutropenia severity, ranging from 0 to 4, are identified by the National Cancer Institute's Common Toxicity Criteria (NCI-CTC) [6]. Patients with grade 4 neutropenia (absolute neutrophil count, ANC, $<0.5\times10^9$ cells/l), the most severe and dangerous grade, are at greatest risk of developing severe infections. In particular, patients with febrile neutropenia (FN), i.e., both grade 4 neutropenia and a fever greater than 38.3°C, are often hospitalized and placed on antibiotics to prevent sepsis [7, 8].

When neutropenia requires hospitalization, it stands to reason that the neutropenia would have detrimental effects on patients' quality of life (QoL). Nevertheless, there is little empirical evidence to support this inference, with even less being known about QoL changes associated with different neutropenia grades. It has been observed in some studies that social, physical, and global functioning may be significantly impacted by chemotherapy [9–12]. Fortunately, once patients complete chemotherapy, QoL scores generally return to baseline levels [10, 12]. Common adverse events of chemotherapy include dehydration, nausea, anorexia, and asthenia; all of these have been observed to be worse during periods of FN [13]. Glaspy et al. specifically noted that, compared to patients without FN, patients with FN exhibited a higher incidence, a longer duration, and/or a greater severity of the following adverse events: abdominal pain, anorexia, asthenia, dehydration, fatigue, rigors, and vomiting. They noted that similar nonsignificant trends were observed among patients with grade 4 neutropenia without fever. Even in the absence of fever and infection, behavioral precautions to minimize infection risk may lead to reduced social and emotional support that can affect QoL.

This investigation was primarily exploratory in nature. We sought to expand understanding of the relationship between QoL and chemotherapy-induced neutropenia (CIN). This prospective, single-center, single-arm, observational study evaluated QoL relative to the severity of neutropenia experienced during the first cycle of myelosuppressive chemotherapy. Because the primary clinical risks of neutropenia are associated with the most severe grade, it was specifically hypothesized that patients who experienced grade 4 neutropenia during the chemotherapy cycle would experience greater decreases in QoL than patients who experienced either no or mild neutropenia.

## Patients and methods

The protocol was approved by the Western Institutional Review Board (Olympia, Washington). Patients provided informed consent before completing any study procedures.

### Patient population

Eligible patients were adults (≥18 years old) with any cancer type who were scheduled to receive the first 21-day chemotherapy cycle at the full dose at the West Clinic (a regional community oncology center in Memphis, Tenn.) using one of five regimens: docetaxel; CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone); carboplatin-paclitaxel; carboplatin-gemcitabine; carboplatin-docetaxel. Patients had to be physically and mentally able to complete the questionnaires and had to be fluent in English. To prevent confounding effects, patients were excluded if they were scheduled to receive growth factor. Patients were also excluded if they were enrolled in another clinical trial or had a life expectancy <3 months.

### Procedures

Patients visited the clinic on days 0, 7, 14, and 21 of the chemotherapy cycle for assessment of vital signs, complete blood count (CBC) with differential, and QoL assessment. CBC was also obtained on day 10. During each clinic visit, patients completed QoL assessments before being informed of their CBC results. ANC was calculated based on the CBC results. Neutropenia grade was determined using the NCI-CTC [6]. The Eastern Cooperative Oncology Group (ECOG) performance status score was assessed. Patients were asked to record their body temperature daily between the hours of 7:00 pm and 9:00 pm. Semistructured interviews were administered by research staff on days 0, 7, 14, 21, and 28 of the chemotherapy cycle to assess qualitative information on patient functioning. Once a patient experienced grade 2 CIN or worse (ANC $<1.5\times10^9$/l), neutropenia-related questions were added to that patient's interviews until the end of the study. Results from these qualitative interviews will be reported separately.

### Measures of QoL

Because this study was exploratory, four QoL instruments were employed to investigate the impact of neutropenia. We selected measures that covered physical symptoms related to grade 4 CIN. We also included measures of social, psychological, and family functioning because severe CIN can require social restrictions that might in turn lead to isolation and increased distress.

*Medical Outcomes Study SF-36 Health Survey* The Medical Outcomes Study SF-36 Health Survey (SF-36) is a multidimensional measure of health-related outcomes and quality of life [14, 15]. SF-36 measures eight domains: (1) Physical Functioning (ability to perform physical activities such as bathing, dressing, and climbing stairs); (2) Role-Physical (problems with work and daily activities); (3) Bodily Pain (intensity of pain and limitations); (4) General Health (subjective evaluation of personal health and outlook on future); (5) Vitality (degree of energy as contrasted with malaise); (6) Social Functioning (ability to perform normal social activities); (7) Role-Emotional (problems with work and daily activities caused by emotional problems; (and 8) Mental Health (freedom from anxiety and depression and overall well being). SF-36 contains two global quality of life scales: the Physical Health Summary Scale (PCS) and the Mental Health Summary Scale (MCS).

*Cancer Care Monitor* The Cancer Care Monitor (CCM) is a reliable and valid measure of six domains of patient symptoms and functioning, and it also provides an overall QoL index [16]. The domains measured are: (1) Physical Symptoms; (2) Treatment Side Effects; (3) Distress; (4) Despair; (5) Impaired Ambulation; and (6) Impaired Performance. Scores are normalized *t* scores and higher scores indicate worse symptom burden, except for QoL where higher scores indicate better QoL.

*Hospital Anxiety and Depression Scale* The Hospital Anxiety and Depression Scale (HADS) is a measure of distress and provides separate scores for scales that represent autonomic anxiety and features of depression [17]. Validity studies have shown that the HADS has good discriminate and convergent validity, although there is some question as to the uniqueness of the anxiety and depression scales [18, 19]. Higher scores indicate greater distress.

*Psychosocial Adjustment to Illness Scale–Self Report* Psychosocial Adjustment to Illness Scale–Self Report (PAIS-SR) is a 46-item multidimensional inventory to assess psychological and social adjustment of medical patients, and it has been shown to be sensitive to disease progression in cancer patients [20]. Two of the seven PAIS-SR scales, comprising five items each, were repeated at each visit in this study: Extended Family Relationships (nature and frequency of contacts with family members) and Social Environment (interest and participation in social activities). Higher scores reflect better patient-reported family interactions and social participation.

### Statistical methods

The neutropenia status (grade 0–3 versus grade 4) of each patient was determined in each week of the cycle according to the lowest measured or estimated ANC in that week. ANCs were estimated for days on which they were not measured by linearly interpolating between the measured ANC values obtained on days 1, 7, 10, 14, and 21. If a measured or interpolated ANC value was $<0.5\times10^9$/l, the patient was classified as having grade 4 neutropenia in that week.

To clarify the direction of change and to simplify interpretation, the 19 measures were transformed (when necessary) so that a negative change in the measure from baseline to the point of observation corresponded to a decline in QoL whereas a positive change represented an improvement in QoL.

Differences in demographics and baseline measurements between patients who experienced grade 4 neutropenia versus others (grade 0–3) in cycle 1 were tested using the chi-squared test for categorical variables and the *t*-test for continuous variables.

Generalized estimating equations (GEE) were employed to analyze the impact of grade 4 neutropenia on changes during the first chemotherapy cycle. This approach to the analysis of the weekly QoL measurements facilitated an examination of the impact of grade 4 neutropenia in any week of the cycle after controlling for baseline covariates. The GEE approach also allowed subjects with complete baseline data but incomplete post-baseline ANC and QoL assessments to be included. Because only one patient experienced grade 4 neutropenia in week 3, the GEE model could not be fitted or yielded unstable estimates in many analyses. Consequently, the GEE analyses presented here exclude week 3 of the cycle.

The GEE method was used to model the change in each measure from baseline to the end of weeks 1 and 2 using age, sex, and baseline QoL (SF-36 Physical and Mental Summary measures and the QoL measure being analyzed) as fixed (baseline) covariates, and week of cycle, neutropenia status (grade 4 versus grade 0–3) over the past 7 days, and their interaction as time-dependent covariates. Mean changes from baseline in QoL measures were estimated according to neutropenic status using the GEE model with coefficients based on the mean age of all patients and the actual proportion of patients at each level of the other covariates.

Because scatterplots showed a nonlinear relationship between baseline and post-baseline QoL scores, the baseline score of the QoL measure being analyzed was included in the GEE model as a covariate with three levels: the lowest 10% of scores, the highest 10% of scores, and the middle 80% of scores. The baseline SF-36 physical and mental health summary scores were coded in the same manner.

No adjustments for the overall type I error rate were applied to significance tests of GEE model effects. Accordingly, because 19 different measurements were analyzed, the results described as "significant" should be interpreted as "nominally significant" at the 0.05 level and suggestive of a possible relationship.

## Results

### Sample characteristics and neutropenia status

A total of 80 patients were enrolled, the first on 18 April 2001 and the last on 29 November 2001. Of these 80 patients, 71 completed the first cycle; 9 withdrew from the study, none because of neutropenia. Reasons for withdrawal included: three terminally ill patients discontinued treatment; three lived far away and did not want to make the necessary extra trips to the clinic; and three withdrew without explanation. No significant or otherwise meaningful differences in age, sex, or baseline QoL scores were observed between those who did and did not complete the study. None of the nine patients who withdrew completed post-baseline QoL assessments.

**Table 1** Characteristics of 71 patients completing firstcycle chemotherapy

| Characteristic | *N* (%) |
|---|---|
| Mean (SD) age at entry (years) | 62.0 (13.3) (range 27–86) |
| Women | 44 (62) |
| Men | 27 (38) |
| Caucasian, not Hispanic | 62 (87) |
| African American | 9 (13) |
| Marital status | |
| Single | 6 (9) |
| Divorced | 3 (4) |
| Widowed | 9 (13) |
| Remarried | 1 (1) |
| Married | 52 (73) |
| Education | |
| Some high school | 11 (16) |
| High school diploma | 26 (37) |
| Some college | 17 (24) |
| College diploma | 12 (17) |
| Some graduate school | 2 (3) |
| Graduate degree | 3 (4) |
| Employment status at entry | |
| Employed full time | 15 (21) |
| Retired | 28 (39) |
| On medical leave | 9 (12) |
| Disabled (unable to work) | 4 (6) |
| Homemaker | 3 (4) |
| Unemployed | 5 (7) |
| Would not disclose | 7 (10) |

Patient characteristics are shown in Table 1. The distribution of the chemotherapy regimens across cancer types is shown in Table 2. On average, patients were diagnosed 10 months (SD 22 months) before enrollment. Most patients (71%) were receiving first-line chemotherapy.

Of the 71 patients available for evaluation, 33 experienced grade 4 neutropenia episodes with 14 (20%) in week 1, 25 (35%) in week 2, and 1 (1%) in week 3. Relatively few patients (6 of 71, 9%) experienced grade 4 neutropenia during more than 1 week of the cycle. Two patients experienced FN (concurrent grade 4 neutropenia and temperature ≥38.2°C) in cycle 1. No patients were hospitalized for FN.

## Baseline differences and neutropenia status

There were no statistically significant differences between patients who experienced grade 4 neutropenia and those who did not with respect to age, sex, or the baseline SF-36 physical and mental well-being summary scores. Of the 19 scales used to measure changes in QoL across the full cycle, only SF-36 Physical Function ($P$=0.006) and Role Emotional ($P$=0.028) scales and the PAIS Extended Family Relationships ($P$=0.029) scales were significantly different at baseline for patients who experienced grade 4 neutropenia versus others. The means (SD) of the Physical Function, Role Emotional, and Extended Family Relationships scale scores for grade 4 CIN patients were 58.4 (28.1), 52.9 (42.2), and 47.9 (13.3), respectively, compared with 39.9 (26.3), 31.6 (40.7), and 54.2 (9.9), respectively, for patients not experiencing grade 4 CIN. In each case, patients who went on to experience grade 4 CIN had more favorable QoL scores at baseline compared with those who did not experience grade 4 CIN.

## Impact of neutropenia on changes in QoL

Patients included in the GEE analysis of each QoL scale had to have complete baseline covariate data, at least one post-baseline QoL assessment in week 1 or week 2, and observed or interpolated ANC measurements in the same week as the post-baseline QoL assessment. Of the 71 evaluated patients, 69 met these criteria for all SF-36 and HADS scales, 68 for both PAIS scales, and from 64 to 68 for the different CCM scales.

The first step in the analysis of each QoL measure was to determine the need for the interaction term involving the neutropenia status and week of cycle variables. The interaction term was not significant for any of the 19 GEE models ($P$>0.05), indicating that, for all scales, the relationship between QoL change and neutropenia status was similar in weeks 1 and 2 of the cycle. Accordingly, the interaction term was excluded from each GEE model.

**Table 2** Number of patients by cancer type and chemotherapy regimen

| Cancer type | Chemotherapy regimen | | | | |
|---|---|---|---|---|---|
| | Docetaxel | CHOP | Carboplatin-paclitaxel | Carboplatin-gemcitabine | Carboplatin-docetaxel |
| Lung | 4 (16.0%) | – | 5 (20.0%) | 6 (24.0%) | 10 (40.0%) |
| Breast | 13 (92.9%) | – | 1 (7.1%) | – | – |
| Ovarian | 2 (16.7%) | – | 9 (75.0%) | – | 1 (8.3%) |
| Lymphoma | 1 (11.1%) | 8 (88.9%) | – | – | – |
| Prostate | 3 (100%) | – | – | – | – |
| Other[a] | – | – | 3 (37.5%) | 2 (25.0%) | 3 (37%) |

[a]Includes bladder, stomach, esophageal, cervical, endometrial and other unspecified tumor types

**Table 3** Adjusted mean change from baseline in QoL measures and effect size contrasts by neutropenia severity in weeks 1 and 2 of the firstcycle of chemotherapy

| Measure | Subscale | Grade 4 in past week Adjusted mean (SE) | Grade 0–3 in past week Adjusted mean (SE) | Absolute effect size | *P* value |
|---|---|---|---|---|---|
| Cancer Care Monitor | General Physical Symptoms | −1.37 (1.35) | −1.00 (0.85) | 0.03 | 0.81 |
| | Treatment Side Effects | −4.94 (1.28) | −3.46 (0.72) | 0.15 | 0.24 |
| | Distress | 1.85 (1.16) | 2.03 (0.80) | 0.01 | 0.89 |
| | Despair | −1.04 (1.21) | 0.51 (0.94) | 0.09 | 0.34 |
| | Impaired Performance | −3.09 (1.20) | −1.70 (0.73) | 0.15 | 0.24 |
| | Impaired Ambulation | 2.74 (2.61) | 2.47 (1.96) | 0.02 | 0.87 |
| | Global Health-related QoL | −2.61 (1.28) | −1.89 (0.67) | 0.08 | 0.60 |
| SF-36 | Physical Functioning | −3.75 (3.11) | −1.09 (2.09) | 0.12 | 0.37 |
| | Role–Physical | −28.55 (4.68) | −24.78 (3.89) | 0.11 | 0.25 |
| | Bodily Pain | −5.15 (3.51) | 4.61 (1.82) | 0.37 | 0.01 |
| | General Health | −3.84 (2.41) | −2.84 (1.60) | 0.06 | 0.67 |
| | Vitality | −4.24 (3.14) | −1.27 (1.91) | 0.15 | 0.38 |
| | Social Functioning | 1.54 (3.93) | 1.70 (2.96) | 0.01 | 0.97 |
| | Role–Emotional | −1.01 (7.91) | −1.43 (5.67) | 0.00 | 0.95 |
| | Mental Health | 0.85 (1.86) | −0.02 (1.50) | 0.06 | 0.65 |
| HADS | Anxiety | 0.22 (0.32) | 1.03 (0.23) | 0.28 | 0.03 |
| | Depression | −0.54 (0.49) | −0.26 (0.30) | 0.07 | 0.60 |
| PAIS | Extended Family | 3.89 (1.63) | 3.21 (1.34) | 0.05 | 0.68 |
| | Social Environment | −2.66 (1.20) | 0.37 (1.13) | 0.28 | 0.04 |

*Note:* The statistics presented are from each GEE model of the relationship between neutropenia severity and change in QoL adjusted for sex, age, baseline QoL, and week of cycle. *P* values are for the test of the neutropenia severity variable in the GEE model. Negative (positive) adjusted mean values indicate worsening (improvement) of QoL or symptom burden compared to baseline. Effect sizes are calculatedas the absolute difference between the grade 4 and grade 0–3 adjusted means divided by the pooled standard deviation

The GEE analyses indicated that for 3 of 19 measures, QoL changes from baseline were significantly less favorable when patients experienced grade 4 neutropenia in the past 7 days compared to when they did not (grade 0–3). Examination of the adjusted means (Table 3) indicated that, on average, Bodily Pain (SF-36) worsened when patients experienced grade 4 neutropenia in the past 7 days but improved when they did not ($P$=0.01). Anxiety (HADS) improved overall but less so when patients experienced grade 4 neutropenia in the past 7 days ($P$=0.03). Social Environment (PAIS) worsened when patients experienced grade 4 neutropenia in the past 7 days but improved when they did not ($P$=0.04).

Though not significant, adjusted means for 12 of the remaining 16 measures exhibited a similar pattern of less favorable QoL change for patients experiencing grade 4 neutropenia in the previous 7 days compared to those who did not. The exceptions were Impaired Ambulation (CCM), Extended Family (PAIS), and Role–Emotional and Mental Health (SF-36).

The issue of the clinical meaning of this pattern is addressed in Table 3 where effect sizes for the contrast between the two different neutropenia severities are presented. Although there is no broad consensus regarding how to quantify clinically important differences and clinically important changes in QoL measures [21], one approach is to examine effect sizes for measures that have also been benchmarked to laboratory findings and/or disease status variables. The SF-36 has been so evaluated, and the effect size for the Bodily Pain scale observed in this study, 0.37, exceeds criteria for minimal clinically important differences (0.09 to 0.28) on SF-36 scales [22]. The other two statistically significant differences detected in this study, Anxiety (HADS) and Social Environment (PAIS), also correspond to effect sizes that are clinically significant.

## Discussion

This prospective investigation of QoL changes associated with grade 4 neutropenia during the first chemotherapy cycle provides evidence of an association between grade 4 neutropenia and declines in QoL. This is supported by the finding that for three QoL measures, changes from baseline were significantly less favorable when patients experienced grade 4 neutropenia in the past 7 days compared to when they did not (grade 0–3), and by the observation of a similar, but non-significant, trend for 12 of the 16 other measures.

Poorer outcomes with respect to pain, anxiety, and social contacts were observed with grade 4 neutropenia. SF-

36 Bodily Pain was worse compared with baseline when patients experienced grade 4 neutropenia in the past week. In contrast, pain was improved when patients did not experience grade 4 neutropenia in the past week. This should not be surprising given some of the symptoms associated with grade 4 neutropenia such as mucositis and 'flu-like symptoms [23]. Patients experiencing grade 4 neutropenia during the previous 7 days exhibited less improvement in anxiety, described by the HADS Anxiety measure, compared with patients without grade 4 neutropenia. Like most other measures of anxiety, the HADS measures generalized distress. The analysis of the PAIS Social Environment measure indicated that, compared to baseline, social contacts and involvement scores decreased more for patients experiencing grade 4 neutropenia in the past week than for those who did not. Patients with severe neutropenia who remain on an outpatient level of care often must restrict contact with others as a precaution against infection. Whether due to lack of energy and stamina or to specific physician-ordered precautions such as reduced contact with people, the experience of grade 4 neutropenia in this study was associated with a significant reduction in social activity.

It should be noted that this study did not include a substantial number of patients experiencing FN, which presumably would produce the most dramatic effects on QoL. Fever itself is associated with negative physical symptoms and decreased functioning. The hospitalization that frequently occurs with FN represents a marked change over a broad range of daily functioning.

Of the 12 scales that showed a trend toward less favorable QoL for patients with grade 4 neutropenia, 6 were within the range of some conventions for minimally clinically important differences by effect size criteria (0.09–0.28) from the SF-36. Generally, these scales measure vitality, physical discomfort, physical function, and physical role limitations. The number of effect sizes that could be judged as clinically meaningful but did not attain statistical significance suggests that the study sample size was inadequate to provide sufficient statistical power to detect potentially important decrements in QoL associated with grade 4 neutropenia.

A total of 19 QoL scales were analyzed using the GEE method. We decided not to employ alpha adjustment procedures to significance tests for two reasons. First, because this study was exploratory and not driven by hypotheses regarding specific QoL scales, no a priori hierarchy existed for conducting sequential inference tests. Second, because of the correlation among scales, the choice of an alpha adjustment procedure was not straightforward, though it was clear that approaches such as a Bonferroni correction, which assumes independence among QoL measures, would be exceedingly conservative. That said, approximately one of the *P*-values out of the 19 QoL analyses conducted would have been expected to be less than 0.05 by chance alone.

In addition, this study was correlational. Whereas correlation is necessary to establish causation, it is not sufficient to conclude that the downward trends in QoL observed were caused by neutropenia. Neutropenia may exhibit temporal relationships with other chemotherapy side effects. Future prospective studies should be designed to provide greater confidence that any observed relationship between neutropenia and QoL is one in which neutropenia acted directly, or through a mediating variable, on QoL. One such design would be to include QoL measures in a randomized clinical trial where colony-stimulating factors (CSF) are used either at the outset or not at all. With such a design, an a priori comparison of these two arms that shows significantly less neutropenia and significantly better QoL with CSF use would provide strong evidence that QoL can be improved by reducing the risk of CIN and demonstrate a causal link between neutropenia status and QoL change. This study did not control for chemotherapy dose or schedule, and the limited numbers of patients within the various schedules and dose ranges of chemotherapy prohibited consideration of those factors in the analysis. Future studies should control for factors such as chemotherapy dose and schedule, expected myelosuppression, and the expected timing of the ANC nadir.

A final concern is that patients may have been influenced by knowledge of their neutropenia history. Patients were blinded to their current neutropenia status when completing objective QoL measures at each visit but were aware of the previous study visit laboratory results. Blinding patients to current neutropenia status during the completion of QoL measures may have minimized reporting of psychological distress with awareness of neutropenia, but the impact of awareness of previous neutropenia status may have had the opposite effect. Furthermore, the subset of patients who experienced grade 2 neutropenia or higher were interviewed following the visit regarding their qualitative experiences with neutropenia, and it is not known what effect these interviews might have had. Future studies may prospectively vary study methods to determine the role patient awareness may play in responses to QoL measures.

This study suggests that there may be a QoL decrement associated with development of grade 4 neutropenia; that the decrement is greatest for physical pain, anxiety, and social interaction; and that the decrement is measurable up to a week after the grade 4 neutropenia event. Future studies should be designed to confirm these preliminary findings and to investigate whether this decrement is greater for those who have longer durations of grade 4 neutropenia or who develop fever and infection. Further research into the impact of neutropenia on QoL may improve the care of cancer patients receiving myelosuppressive chemotherapy.

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