Inverse relationship between reduced fatigue and severity of anemia in oncology patients treated with integrative medicine: understanding the paradox

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Abstract

Objective To assess the impact of integrative medicine (IM) on cancer-related fatigue in patients undergoing chemotherapy for early and advanced breast and gynecological (ovarian, endometrial, and cervical) cancer.

Methods Patients reporting significant levels of fatigue (on the Edmonton Symptom Assessment Scale (ESAS), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), or Measure Yourself Concerns and Wellbeing questionnaire (MYCAW)) were offered complementary and integrative medicine (CIM) treatments in addition to standard supportive care. Patients who did not undergo IM treatments were designated as controls. Attending at least five CIM treatments less than 30 days between each session was considered as high adherence to integrative care (AIC).

Results Of 258 eligible patients reporting significant fatigue, follow-up assessment at 6 and 12 weeks was considered optimal for 120 patients in the intervention group and for 64 controls; 88 of treated patients found to be adherent to the IM intervention. At 12 weeks, ESAS (P < 0.001) and EORTC (p = 0.001) scores for fatigue improved more significantly in treated patients, with a higher percent with optimal relative dose intensity in the AIC subgroup, both at 6 weeks (P = 0.002) and at 12 weeks (P < 0.001). IM treatment was paradoxically associated with a greater decrease in hemoglobin levels at 12 weeks (P = 0.016), more so in the AIC subgroup (P = 0.024).

Conclusion Integrative medicine program may alleviate cancer-related fatigue in patients with breast and gynecological cancer undergoing chemotherapy.

Keywords Cancer-related fatigue • Integrative medicine • Complementary medicine • Relative dose intensity • Quality of life • Anemia

Introduction

Fatigue is an often reported concern among patients undergoing chemotherapy for early- and advanced-stage breast cancer, persisting for as long as a year after completing treatment [1, 2]. Cancer-related fatigue (CRF) is associated with factors related to the tumor as well as to chemotherapy-related toxicities (anemia, gastrointestinal symptoms with weight loss, etc.), emotional concerns, and sleep-related difficulties [3, 4]. Conventional treatments for CRF are of limited benefit and involve drug (e.g., methylphenidate, modafinil) and non-drug interventions (e.g., physical exercise), as well as treating factors which may exacerbate symptoms (e.g., iron supplementation for anemia) [5, 6].

Complementary and integrative medicine (CIM) is becoming increasingly prevalent among oncology patients, and more and more oncology centers provide CIM as part of their palliative service [7]. Several CIM modalities have been shown in clinical research to help reduce the severity of CRF, including randomized controlled trials which examine the use of herbal medicinal products for this indication. The findings of this research support the use of astragalus (Astragalus
membranaceus) in patients with non-small cell lung cancer undergoing treatment with cisplatin and vinorelbine [8], patients with advanced pancreatic cancer treated with subcutaneous injection of the herb mistletoe (Viscum album) [9], and cancer survivors treated with ginseng (Panax quinquefolius), all of which have shown to significantly reduce CRF-related symptoms and concerns [10]. Other CIM therapies have also been found to be of benefit, such as acupuncture [11], acupuncture pressure [12], infrared laser moxibustion [13], Qigong [14], and Tai Chi [15]. Pragmatic controlled, non-randomized trials examining an integrative oncology program, where CIM therapies are provided within a conventional oncology setting, has shown that a patient-tailored CIM approach may reduce fatigue in patients reporting chemotherapy-related gastrointestinal-related concerns [16, 17]. However, the heterogeneity of the study populations, as well as the inclusion of CRF only as a secondary study outcome, precludes reaching any conclusions on the effectiveness of such a program. The current study is purposed to examine the effect of a CIM approach in a specific population of female patients diagnosed with breast and gynecological cancer, who reported severe CRF-related concerns following chemotherapy.

Methods

Study design

The study was designed using a pragmatic (controlled, non-randomized) methodology, as part of a registry protocol currently taking place at the Lin and Zebulon Medical Centers, Clalit Healthcare Services (CHS), Israel [18]. Patients undergoing chemotherapy at the CHS outpatient oncology clinic are referred to the service’s Integrative Oncology Program (IOP) by one of their oncology health care practitioners (HCP). The IOP provides patients with a wide range of CIM modalities included in its supportive and palliative care service.

Study population

Study recruitment took place from June 2013 to May 2016. Patients undergoing adjuvant, neo-adjuvant, or palliative chemotherapy for early- to late-stage gynecological or breast cancer were deemed eligible for inclusion. The study nurse informed all potential recruits about the IOP service and about the possibility of referral to CIM consultation provided by physician trained in supportive cancer care and CIM (henceforth integrative physician (IP)), throughout the study period. Recruited patients attending the initial IP physician consultation were allocated to the intervention arm of the study; those who had been informed of their ability to be referred but were not interested were designated as controls. Patients in the intervention arm of the study were further divided, in accordance with their adherence to the integrative care (AIC) program. Attending at least five CIM treatments less than 30 days between each session was considered as high AIC. Both intervention and control groups received standard supportive care.

CIM treatment program

CIM treatment plan was constructed during the IP physician consultation based on the patient’s expectations and research evidence concerning risks and effectiveness of the planned CIM treatments, in accordance with clinical guidelines [19]. Following consultation, CIM treatments were delivered on a weekly basis, for a period of 12 weeks, and include manual modalities (e.g., acupuncture), dietary supplement consultation, and mind-body-spirit and manual-movement therapies. For those patients identified during the IP consultation as suffering from CRF-related symptoms and concerns, the patient-tailored CIM regimen includes fatigue-specific interventions (e.g., acupuncture at the St-36 point) as well [20].

Assessment of fatigue

QOL and CRF-related symptoms were assessed at baseline—by the IP for patients in the intervention arm and by the study nurse for patients in the control group—with re-assessment conducted at 6 and 12-week follow-up appointments. The severity of these symptoms was measured using the Edmonton Symptom Assessment Scale (ESAS) [21, 22], the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) [23], and the Measure Yourself Concerns and Wellbeing (MYCAW) questionnaire [24]. Fatigue severity was assessed in the ESAS tool by item #2 (from 0 to 10) and in EORTC with items #12 (“have you felt weak?”) and #18 (“Were you tired?”), with scores ranging from 0 to 100.

Patients were considered to have significantly severe CRF-related symptoms if meeting one or more of the following criteria: (1) ESAS score of ≥ 7 for fatigue, this with the goal of identifying patients with significant fatigue [25]; (2) a score of ≥ 3 on at least one of the EORTC questions for fatigue [26]; and (3) a score of ≥ 5 on at least one of the MYCAW main concerns, where fatigue was listed as one of the two most important of these concerns. The impact of the CIM treatment program on fatigue scores was assessed using the ESAS and EORTC fatigue-related scores, which were established as the study’s primary outcome variables, between initial and the 12-week assessment. ESAS and EORTC were used in order to address QOL-related concerns using different time frames: the ESAS asking patients about the last 24-h period and the EORTC about the last 7 days period. The MYCAW tool was used primarily to identify patients suffering from CRF, as well
as being used as part of the qualitative assessment of the CIM treatment program.

**Additional factors influencing fatigue: hemoglobin levels, adherence to chemotherapy regimen**

In order to assess factors which may potentially influence the severity of CRF-related symptoms and concerns, the study examined the values of patient hemoglobin levels, taken routinely as part of patients’ oncology follow-up. Blood counts were included in the analysis if they had been performed within 120 h prior to or 48 h following the IP follow-up visit.

Adherence to the planned chemotherapy regimen using the relative dose intensity (RDI) was also assessed and was calculated from initial assessment to the 6 and 12-week visits [27]. RDI = 1 was regarded as completion of the planned chemotherapy dosage and time schedule.

**Optimality of assessment between baseline and follow-up assessments**

Optimality of assessment was deemed necessary in order to ensure that a similar time interval was kept between the administration of chemotherapy (baseline) and the 6 and 12 weeks assessments. Assessment was considered to be optimal if it took place within a similar interval of time between the administration of chemotherapy and the follow-up visit (≤ 72 h for adjuvant or neo-adjuvant chemotherapy difference; up to 7 days in palliative setting) at both baseline and follow-up assessments, provided that the chemotherapy regimen remained unchanged.

**Statistical analysis**

Calculated sample size aimed to achieve alpha-error of 0.05 and beta-error of 0.2 suggested that 80 patients would be needed in each study arm for detection of 20% difference in ESAS scales. Fisher’s exact and t test were used in analysis of categorical or continuous variables and the Mann-Whitney U test for abnormal distribution.

Assessment of RDI change comparing baseline to the 6- and 12-week assessments was implemented using the McNemar-Bowker tests for categorical variables and the Wilcoxon signed-rank test for continuous variables. Correlations between ESAS fatigue and EORTC fatigue scores and hemoglobin levels between baseline and follow-up assessments were performed using a two-way repeated measure ANOVA separately for the control and treatment and groups.

A multivariate logistic regression model was designed to predict a decrease in hemoglobin levels between baseline and 12 weeks, examining variables of the following: cancer site and recurrence, metastasis, chemotherapy setting (adjuvant and neo-adjuvant vs. palliative), group allocation (treatment vs. control), and RDI.

**Ethical considerations**

The Carmel Medical Center Helsinki Committee Ethics approved the study (registered at ClinicalTrials.gov NCT01860365). Participation was voluntary, and no payment or other incentive was offered as an incentive.

**Results**

**Study groups**

Significant fatigue-related symptoms and concerns were assessed in 258 patients undergoing chemotherapy (Fig. 1). Of these, 168 underwent an IP consultation and were designated to the treatment arm. At 12 weeks, data were obtained for 100 patients in the intervention group, of whom 81 were regarded as adherent to the integrative treatment program (AIC subgroup). The remaining 90 patients with significant fatigue were not interested in undergoing the IP consultation and subsequent integrative treatments and were allocated to the control arm of the study. At 12 weeks, data were obtainable for 63 of the patients in this control arm.

**Baseline characteristics of study groups**

Age and additional demographics (residence location, religiosity, religion, country of birth) were similar in both groups, though the treatment arm had elevated levels of income (P = 0.001), Hebrew speaking (P = 0.006), and education (P < 0.001) (Table 1). Both groups were similar regarding the sites of their cancer (breast vs. gynecological cancer), rates of cancer recurrence, metastasis, and chemotherapy setting (adjuvant/neo-adjuvant compared with palliative chemotherapy). Yet, the intervention group reported more of alternative/complementary medicine use, for either current cancer-related issues (P < 0.001) or for general concerns in the past (P = 0.002).

When comparing the intervention arm subgroups, it was found that patients in the AIC and non-AIC subgroups had similar demographic and oncology parameters. However, patients in the AIC subgroup reported more of use of alternative/complementary medicine associated with cancer diagnosis/treatment (P = 0.01).

**CIM intervention modalities**

Of the 120 patients in the treatment arm who were optimally assessed, 100 (83%) were treated with acupuncture.
Other CIM modalities which were administered during the study period included mind-body-spirit therapies (93, 77%), touch/movement therapies (83, 69%), and herbal/nutritional interventions (76, 63%). Most patients (107, 89%) had been treated simultaneously with at least two of the above CIM therapies.

Correlation between hemoglobin levels, RDI, and fatigue (treatment vs. control groups)

Table 2 presents the patient-reported outcome scores for both treatment and control groups. Baseline scores for fatigue were similar in both groups on ESAS and EORTC, as were the initial hemoglobin levels. Between-group analysis indicated a significantly improved fatigue in the intervention group compared with controls on ESAS ($P < 0.0001$) and on EORTC ($P = 0.001$) at the 12-week assessment (Fig. 2). In addition, ESAS scores for drowsiness at 12 weeks improved significantly in the intervention group and worsened in controls (between-group analysis, $P < 0.0001$). At the same time, a greater decrease in hemoglobin levels was reported in the treatment arm of the study at 12 weeks ($P = 0.016$). RDI from the initial the 12-week assessment was similar between the two groups.

A two-way repeat measures ANOVA test found that the decrease in hemoglobin levels correlated in both groups with fatigue grades on both ESAS ($P < 0.001$) and EORTC ($P < 0.00001$), between baseline and 6-week assessment, as well as at 12 weeks. However, this correlation was not statistically significant at the 12-week assessment (hemoglobin and ESAS, $P = 0.84$; hemoglobin and EORTC, $P = 0.64$). A logistic multivariate regression model, however, suggested that decreased hemoglobin levels were associated more significantly with CIM treatment ($B = -2.047$, stand error = 0.455, $t = -4.504; P < 0.001$), though no association was found with respect to the site of the cancer, the presence of metastasis, the oncology treatment setting, or the patient’s RDI.

Correlation between hemoglobin, RDI, and fatigue (treatment AIC vs. non-AIC subgroups)

Table 3 presents patient-reported outcomes scores for the two treatment subgroups (high compared with low adherence to CIM). Baseline hemoglobin levels were similar in both groups, as were fatigue scores on ESAS, EORTC, and MYCAW. At 12 weeks, the improvement in ESAS and EORTC scores for fatigue was evident in both AIC/non-AIC subgroups. In contrast, hemoglobin levels dropped more significantly in the AIC subgroup ($11.7 \pm 1.5$ to $10.7 \pm 1.3$ vs. $11.8 \pm 1.5$ to $11.7 \pm 1.4$, $P = 0.024$). At the same time, the RDI at 12 weeks was significantly higher in the AIC subgroups (AIC, $0.95 \pm 0.09$; non-AIC, $0.84 \pm 0.18$, $P < 0.0001$).

Safety of the CIM intervention

Of the 120 patients in the intervention arm of the study, only 6 reported mildly severe adverse effects possibly related with CIM. These included one patient who reported persistent pain at the acupuncture point, three patients with localized bleeding, one patient who attributed an increased sense of sadness to a mind-body intervention, and one
patient who reported difficulty with concentration/cognitive function during the treatments.

**Discussion**

In this research, we investigated the effect of a patient-tailored CIM plan on fatigue in patients treated with chemotherapy for breast cancer as well as gynecological malignancies. After 12 weeks in the CIM program, patients in the treatment group reported significant improvement in CRF-related outcomes on the ESAS and EORTC questionnaires when compared to controls. Paradoxically, hemoglobin levels decreased more significantly in the treatment group during this period. Between-group analysis comparing adherent to non-adherent treatment subgroups (AIC vs. non-AIC) showed a significant decrease in hemoglobin levels in the AIC group, with higher RDI percentages when compared with the non-AIC subgroup.

The paradoxical relationship between reduced CRF-related outcome severity and reduced hemoglobin levels in the adherent CIM-treated group runs counter to previous literature reports. In a study of patients with non-myeloid malignancy undergoing chemotherapy, Gabrilove et al. found a correlation between increased hemoglobin levels resulting from treatment with darbepoetin-alpha and an improvement in fatigue-related outcomes [28]. Gascón et al. assessed fatigue in cancer patients with anemia and concluded that minimal increases or decreases in hemoglobin were associated with parallel changes in patient-perceived fatigue [29]. At the same time, studies which were conducted in a palliative care setting found either no correlation or, at best, only a moderate association between fatigue and hemoglobin levels [30, 31]. While the relationship between anemia and fatigue has not yet been examined in a CIM treatment setting, a study by Chuang et al. did find

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control group, n = 64, n (%)</th>
<th>Intervention groups n = 120 n (%)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>56.7 ± 13.6</td>
<td>57.6 ± 12.6</td>
<td>58.3 ± 12.9</td>
</tr>
<tr>
<td>Language (Hebrew)</td>
<td>31 (48.4)</td>
<td>84 (70.0)</td>
<td>59 (67.0)</td>
</tr>
<tr>
<td>Country of birth (Israeli born)</td>
<td>39 (60.9)</td>
<td>70 (60.3)</td>
<td>53 (63.1)</td>
</tr>
<tr>
<td>Residence (Haifa and suburbs)</td>
<td>70 (62.5)</td>
<td>80 (66.7)</td>
<td>59 (67.3)</td>
</tr>
<tr>
<td>Cancer site, breast (vs. GYN-cancers)</td>
<td>50 (78.1)</td>
<td>81 (67.5)</td>
<td>57 (64.8)</td>
</tr>
<tr>
<td>Cancer recurrence (yes)</td>
<td>18 (28.1)</td>
<td>34 (28.3)</td>
<td>27 (30.7)</td>
</tr>
<tr>
<td>Evidence of metastasis (yes)</td>
<td>25 (39.1)</td>
<td>45 (37.5)</td>
<td>36 (40.9)</td>
</tr>
<tr>
<td>Oncology treatment setting, adjuvant and neo-adjuvant (vs. palliative)</td>
<td>37 (58.7)</td>
<td>79 (65.8)</td>
<td>55 (62.5)</td>
</tr>
<tr>
<td>Education (high-school and academic)</td>
<td>38 (59.4)</td>
<td>104(88.1)</td>
<td>77 (88.5)</td>
</tr>
<tr>
<td>Income (average and below)</td>
<td>56 (93.3)</td>
<td>86 (73.5)</td>
<td>61 (70.9)</td>
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<tr>
<td>Religiosity (secular)</td>
<td>29 (45.3)</td>
<td>61 (51.3)</td>
<td>46 (52.9)</td>
</tr>
<tr>
<td>Religion (Jewish)</td>
<td>42 (65.6)</td>
<td>93 (78.2)</td>
<td>67 (76.1)</td>
</tr>
<tr>
<td>Prior CM use (non-cancer related: yes)</td>
<td>24 (37.5)</td>
<td>75 (62.5)</td>
<td>59 (67.0)</td>
</tr>
<tr>
<td>Cancer-related CM use (yes)</td>
<td>7 (10.9)</td>
<td>73 (60.8)</td>
<td>60 (68.2)</td>
</tr>
</tbody>
</table>

$P^1$ = Control vs. treatment

$P^2$ = AIC vs. non-AIC
a correlation between higher levels of hemoglobin and lower fatigue severity among chemotherapy-treated non-Hodgkin’s lymphoma patients who were being treated with qigong [32]. The relationship between improved fatigue despite reduced hemoglobin levels in CIM-treated patients, which was reported in the present study, needs to be better understood. It is possible, even probable, that the CIM treatments led to better adherence to the chemotherapy regimen (as per RDI), which then led to a greater reduction in bone marrow depression with reduced hemoglobin levels. Our earlier research at the IOP has shown that greater adherence to CIM treatments is associated with better percentages of RDI = 1.0 in patients with breast and gynecological cancers at 6 weeks, though this effect was not found to persist after 12 weeks of treatment [33]. It would thus appear that the findings reflect an interdependent “triangle” of

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Controls, n = 64</th>
<th>Intervention group, n = 120</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score ± SD (median)</td>
<td>Mean score ± SD (median)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Initial assessment</td>
<td>6-week assessment</td>
<td>12-week assessment</td>
</tr>
<tr>
<td>ESAS fatigue</td>
<td>6.5 ± 2.7 (7)</td>
<td>5.7 ± 3.2 (6)</td>
<td>6.9 ± 2.3 (7.5)</td>
</tr>
<tr>
<td>EORTC fatigue</td>
<td>81.8 ± 23.0 (100)</td>
<td>58.8 ± 38.2 (67)</td>
<td>82.2 ± 19.9 (89)</td>
</tr>
<tr>
<td>MYCAW fatigue</td>
<td>4.63 ± 1.5 (5)</td>
<td>4.29 ± 1.40 (5)</td>
<td>5.56 ± 0.66 (6)</td>
</tr>
<tr>
<td>Hb level</td>
<td>11.2 ± 1.6 (11.1)</td>
<td>11.3 ± 1.5 (11.5)</td>
<td>11.7 ± 1.5 (11.7)</td>
</tr>
<tr>
<td>RDI 0–6 weeks</td>
<td>0.92 ± 0.13 (1)</td>
<td>0.90 ± 0.14 (1)</td>
<td>0.89 ± 0.14 (0.95)</td>
</tr>
<tr>
<td>RDI 0–12 weeks</td>
<td>0.89 ± 0.14 (0.95)</td>
<td>0.92 ± 0.13 (1)</td>
<td>0.89 ± 0.14 (0.95)</td>
</tr>
</tbody>
</table>

\(P^1\) compared scores in initial visit between intervention group and controls
\(P^2\) score changes from initial to 6-week assessment (within intervention group)
\(P^3\) score changes from initial to 6-week assessment (within control group)
\(P^4\) score changes from initial to 6-week assessments (between intervention and control groups)
\(P^5\) score changes from initial to 12-week assessment (within intervention group)
\(P^6\) score changes from initial to 12-week assessment (within control group)
\(P^7\) score changes from initial to 12-week assessments (between intervention and control groups)

ESAS the Edmonton Symptom Assessment, EORTC the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, MYCAW the Measure Yourself Concerns and Wellbeing, Hb hemoglobin level (g/dL), RDI relative dose intensity

Table 2  Within- and between-group changes in outcome measures in control and treatment groups
correlating factors: patient-reported fatigue, hemoglobin, and RDI. Understanding this interaction is made even more complex by the clinical setting in which the CIM program takes place, which is characterized by many potential confounders such as other fatigue-associated QOL outcomes (e.g., anxiety, appetite loss, insomnia) and widely diverse supportive care strategies (e.g., blood transfusions, erythropoietin treatment). It is therefore of utmost importance that future research address each of these factors on their own, as well as the interaction between them.

There are a number of limitations to the present study which need to be addressed in future research before any conclusions regarding the place of integrative medicine in cancer care can be reached. First, a selection bias may have been created by the requirement that participants receive a structured referral from their health care providers to the initial IP consultation. And while the treatment and control groups had similar demographic and cancer-related characteristics at baseline, the intervention group had higher rates of prior use of alternative/complementary medicine. In addition, the question as to why the control group did not wish to undergo an integrative physician consultation or CIM treatments (despite being provided free of charge) needs to be addressed in future research. The heterogeneous patient population with its variation in cancer localization (localized vs. metastatic) and chemotherapy settings (adjuvant/neo-adjuvant versus palliative) may have influenced the degree of fatigue, in addition to other QOL-related parameters which may have influenced this outcome. Also, the study protocol was non-randomized, with the control group consisting of patients preferring not to undergo CIM treatments.

In addition to the above, another study limitation is the fact that QOL- and CRF-related symptoms were assessed at baseline and at follow-up by the IP for patients in the intervention arm, as opposed to the study nurse for patients in the control group, leaving room for an examiner-related bias. There was no any attempt to examine the effectiveness of individual CIM modalities on CRF-related outcomes, but rather that of a patient-centered systems approach, in which CIM therapies are being integrated within supportive cancer care. There was also a lack of monitoring regarding additional supportive care interventions, such as the use of erythropoietin or blood transfusions. In summary, the pragmatic methodology of the present study, while perhaps being more reflective of “real-life” clinical practice, requires a more explanatory approach (i.e., randomized prospective trial) before any conclusions can be reached regarding the place of integrative medicine in cancer care.

In summary, present study findings suggest that a 12-week CIM treatment plan can possibly lead to improved cancer and chemotherapy-related fatigue in patients receiving chemotherapy for breast and gynecological cancer. Paradoxically, this beneficial effect was found to correlate with decreased hemoglobin levels in the CIM-treated patients, most significantly with patients who were adherent to the CIM treatment program. It is possible that the reduced hemoglobin levels reflect a greater adherence to the chemotherapy regimen in the CIM-treated group, a hypothesis which requires further research to verify and better understand.
Table 3  Within- and between-group changes in outcome measures in the treatment subgroups of adherence to integrative care (AIC) vs. non-AIC

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>AIC subgroup, n = 88</th>
<th>Non-AIC subgroup, n = 32</th>
<th>P values*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score ± SD (median)</td>
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<td></td>
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<td></td>
<td>Initial visit</td>
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<td>12-week visit</td>
</tr>
<tr>
<td>ESAS fatigue</td>
<td>6.8 ± 2.1 (7)</td>
<td>5.4 ± 2.3 (5.5)</td>
<td>7.3 ± 2.8 (8)</td>
</tr>
<tr>
<td>EORTC fatigue</td>
<td>81.1 ± 20.8 (89)</td>
<td>69.9 ± 22.9 (67)</td>
<td>85.3 ± 17.3 (89)</td>
</tr>
<tr>
<td>MYCAW fatigue</td>
<td>5.55 ± 0.71 (6)</td>
<td>3.77 ± 1.3 (4)</td>
<td>5.61 ± 0.50 (6)</td>
</tr>
<tr>
<td>Hb level</td>
<td>11.7 ± 1.5 (11.7)</td>
<td>10.9 ± 1.1 (10.7)</td>
<td>11.8 ± 1.5 (12.1)</td>
</tr>
<tr>
<td>RDI 0–6 weeks</td>
<td>0.93 ± 0.13 (1)</td>
<td>0.95 ± 0.09 (1)</td>
<td>0.84 ± 0.15 (0.86)</td>
</tr>
<tr>
<td>RDI 0–12 weeks</td>
<td>0.93 ± 0.13 (1)</td>
<td>0.95 ± 0.09 (1)</td>
<td>0.84 ± 0.15 (0.86)</td>
</tr>
</tbody>
</table>

*1 compared scores in initial visit between intervention group and controls
*2 score changes from initial to 6-week assessment (within intervention group)
*3 score changes from initial to 6-week assessment (within control group)
*4 score changes from initial to 6-week assessments (between intervention and control groups)
*5 score changes from initial to 12-week assessment (within intervention group)
*6 score changes from initial to 12-week assessment (within control group)
*7 score changes from initial to 12-week assessments (between intervention and control groups)

ESAS the Edmonton Symptom Assessment, EORTC the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, MYCAW the Measure Yourself Concerns and Wellbeing, HB hemoglobin level (g/dL), RDI relative dose intensity

Contributions of authors EBA, OD, and NS initiated the trial, collected the data, and analyzed this study. EBA, ISS, OD, and NS planned the study and wrote the manuscript draft. All authors participated in the revision of the manuscript.

Compliance with ethical standards Conflict of interests The authors declare that they have no conflict of interest.

References


