Pre-treatment levels of inflammatory markers and chemotherapy completion rates in patients with early-stage breast cancer

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Statements and Declarations

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Conflict of Interest

HL received research funding by Roche and honoraria from Astra-Zeneca and Eli Lilly and Company in the form of lecture and consultation fees. All other authors have no relevant financial or non-financial interests to disclose.

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Author Contributions

Conceptualization: TS, JFC; Methodology: TS, AH, ES, HL; Formal analysis and investigation: TS, AH, ES; Writing - original draft preparation: TS, JFC; Writing - review and editing: all authors; Funding acquisition: JFC, KN; Resources: AH, HL, KN, SB, ID, TR; Supervision: JFC, KN

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with Ethical Standards

This study was performed in line with the principles of the Declaration of Helsinki and its later amendments. Approval was granted by the Swedish Ethical Review Authority (Dnr 2014/249).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

ABSTRACT

Background

Chemotherapy efficacy is largely dependent on treatment adherence, defined by the relative dose intensity (RDI). Identification of new modifiable risk factors associated with low RDI might improve chemotherapy delivery. Here, we evaluated the association between low RDI and pre-chemotherapy factors, including patient- and treatment-related characteristics and markers of inflammation.

Methods

This exploratory analysis assessed data from 267 patients with early-stage breast cancer scheduled to undergo (neo-)adjuvant chemotherapy included in the Physical training and Cancer (Phys-Can) trial. The association between low RDI, defined as <85%, patient-related (age, body mass index, co-morbid condition, body surface area) and treatment-related factors (cancer stage, receptor status, chemotherapy duration, chemotherapy dose, granulocyte colony stimulating factor) was investigated. Analyses further included the association between RDI and pre-chemotherapy levels of interleukin (IL)-6, IL-8, IL-10, C-reactive protein (CRP) and Tumor Necrosis Factor-alpha (TNF-α) in 172 patients with available blood samples.

Results

An RDI of <85% occurred in 31 patients (12%). Univariable analysis revealed a significant association with a chemotherapy duration above 20 weeks ($p < 0.001$), chemotherapy dose ($p = 0.006$), pre-chemotherapy IL-8 (OR: 1.61; 95% CI (1.01; 2.58); $p = 0.040$) and TNF-α (OR: 2.2 (1.17; 4.53); $p = 0.019$). In multivariable analyses, inflammatory cytokines were significant association with low RDI for IL-8 (OR: 1.65 [0.99; 2.69]; $p = 0.044$) and TNF-α (OR: 2.95 [1.41; 7.19]; $p = 0.007$).

Conclusions

This exploratory analysis highlights the association of pre-chemotherapy IL-8 and TNF-α with low RDI of chemotherapy for breast cancer. IL-8 and TNF-α may therefore potentially help to identify patients at risk for experiencing dose reductions.

Clinical trial number: NCT02473003 (registration: June 16, 2015)

Keywords: Chemotherapy, relative dose intensity, Breast cancer, Tumor Necrosis Factor-alpha, Interleukin-8

INTRODUCTION

Chemotherapy improves survival of patients with cancer substantially [1], with reports showing that cancer-related mortality is reduced by one-third in patients with early-stage breast cancer [2]. Chemotherapy efficacy is determined by the timing of treatment initiation, time intervals between treatment cycles and the dose intensity [3]–[5]. A relative dose intensity (RDI), which describes the ratio between planned and received dose [6], of ≥85% is associated with improved disease-free and overall survival [6]–[8]. Thus, high RDI is critical for optimal chemotherapy administration in the curative setting [9], yet up to a quarter of patients with early-stage breast cancer receive <85% RDI [10], [11]. Reports demonstrate that age (>65 years), body surface area (>2m^2), comorbidities, chemotherapy type, and duration may predict low RDI [8], while administration of granulocyte colony-stimulation factor (G-CSF) is associated with increased RDI [8]. To date, few modifiable risk factors have been identified limiting the potential of clinical action and supportive therapies.

Inflammation is well known to negatively affect cancer diagnosis e.g., by increased cellular proliferation, tumor survival and promotion of metastasis [12]. Further, markers of inflammation in patients with breast cancer have been linked to disease stage [13]–[15] and poor survival [15]–[17]. The effects of inflammation on RDI in patients with breast cancer have previously only been addressed in one study. Yuan and colleagues showed an association between low RDI and pre-

chemotherapy IL-6 and D-Dimer but not CRP [18], while other common inflammatory markers, including TNF-α, IL-8 and IL-10 have not previously been investigated in patients with breast cancer.

The primary aim of the present study was to investigate pre-chemotherapy factors associated with a reduction in RDI with specific focus on the level of pre-treatment ~~concentr~~ations of inflammatory markers (IL-6, IL-8, IL-10, CRP and TNF-α) in patients with early-stage breast cancer undergoing (neo-) adjuvant chemotherapy. Other relevant factors possibly related to RDI included age, BMI, fitness level, co-morbid conditions, chemotherapy dose, G-CSF treatment, and chemotherapy type and duration. As a secondary explorative aim, we investigated the associations between inflammatory markers and chemotherapy-related side-effects leading to treatment adjustment.

PATIENTS AND METHODS

Participants and design

For this study, we included data from participants enrolled in the Physical training and Cancer (Phys-Can study), a Swedish multicenter randomized trial [19]. Briefly, participants were randomized to six months of high (HI) or low-to-moderate intensity (LMI) exercise, with or without additional behavioral support during and after anti-cancer treatment (ClinicalTrials.gov: NCT02473003). For this study, only pre-intervention and treatment-related parameters will be utilized.

Participants were included from Uppsala, Lund and Linköping University hospitals from March 2015 to April 2018. Eligible participants were >18 years, literate in Swedish and recently diagnosed with curable breast (women only), prostate or colorectal cancer. For this study, only data from women with breast cancer receiving (neo-)adjuvant chemotherapy will be presented. Exclusion criteria: stage IIIb-IV cancer, inability to perform basic activities of daily living, cognitive disorders, severe psychiatric disease or other conditions that contraindicate exercise, ongoing treatment for another cancer, BMI <18.5 kg/m^2 or pregnancy [19]. Participants gave written informed consent.

Data collection and outcomes

Information on chemotherapy (type, dose, start and end date), Body Surface Area (BSA) as well as reasons for dose adjustment and treatment-related toxicities was gathered from medical records. Most chemotherapy treatments consisted of six cycles totaling <20 weeks with F/EC (5-Fluorouracil, Epirubicin, cyclophosphamide) and Docetaxel/Paclitaxel. Selected patients (assessed by treating oncologist) with triple negative breast cancer received additional Capecitabine treatment to the standard treatment [20]. Chemotherapy dose was grouped into high (Docetaxel^{100} or F/EC^{100}) and low dose (Docetaxel$^{75\text{-}80}$ and F/EC$^{75\text{-}80}$) or capecitabine-added (Docetaxel and F/EC plus Capecitabine) chemotherapy. Information on tumor stage and immunohistochemistry (estrogen receptor, progesterone receptor, and Her2/neu) was gathered from the Swedish national quality register for breast cancer. For patients with bilateral cancer (n = 7), cancer stage was determined by the more advanced diagnosis (n = 1) while in other cases variables were identical. Background data (age, co-morbid conditions) were self-reported. Chemotherapy completion rates were calculated as mean RDI for the planned treatment [21]. Cardiorespiratory fitness was measured as maximal oxygen uptake (VO_2max [mL/kg/min]) [22].

For analysis of inflammatory markers, pre-chemotherapy blood was collected during the baseline assessment. Blood was collected in EDTA-tubes and centrifuged at 2400g for seven minutes within four hours of collection followed by plasma isolation and storage at -80 °C. Patients were asked not to perform any physical activity on the assessment day. Cytokines (IL-1β, IL-6, IL-8, IL-10 and TNF-α) were measured with the pro-inflammatory panel 1 kit (MesoScaleDiscovery) according to manufacturers´ guidelines in duplicate, blinded and centralized. For IL-1β around 40% of measures were below the detection limit and IL-1β was therefore not included in the analysis. Additionally, inflammatory measures also included CRP, which was performed at the individual inclusion sites [23]. As CRP was measured at individual hospitals, detection limits for CRP were as follows: Uppsala (0.2 mg/L), Lund (0.6 mg/L), Linköping (5 mg/L). For the presented analysis, this resulted in 39% of CRP measurements below the detection limit (<85% RDI: 4/18 (22%); ≥85% RDI: 63/154 (41%)) [23].

Statistical Analyses

The outcome (RDI), was dichotomized to <85% and ≥85%. For univariable analyses (Table 2), the chi-square test of independence was used for categorical variables. For continuous variables (i.e. VO_2max), the Wilcoxon rank sum test was used. For multivariable analyses of odds-ratio (OR), logistic regression was used (Figure 1), including age, BMI, chemotherapy dose and duration as categorical predictors.

For analyses of inflammatory markers, both univariable and multivariable logistic regression was used. Univariable analyses included the dependent variable (RDI) and the log-transformed (base 2) predictor (cytokine concentration). Transformation was performed to limit the influence of right skewed data. Outliers were defined as >3 residual standard deviation of fitted models (note: analysis included one non-extreme outlier in <85% RDI group with TNF-α of 44 pg/mL). The OR reported for inflammatory markers describes the change for every doubling of the inflammatory marker concentration. Multivariable models included the log-transformed cytokine concentration and the categorical variables age (<65 vs. ≥65 years), BMI (<25 vs. ≥25 kg/m^2) and chemotherapy dose (high vs. low dose vs. Capecitabine added) as predictors. For CRP analyses, the deletion approach was chosen i.e., treating below detection limit values as missing [23]. Sensitivity analysis included the substitution approach i.e., values were substituted with the detection limit divided by the square root of two.

For the association between inflammatory markers and chemotherapy related side-effects, univariable logistic regression included the dichotomized outcome (adjustment-type vs. no adjustments) and the log-transformed cytokine concentration. To evaluate if categorical variables differed between participants with and without a blood sample, chi-square test for independence was used. For continuous variables, the Wilcoxon rank sum test was used. Missing data were handled as missing at random. To improve model estimates, missing BMI data (7.5%) was substituted by the median. For analyses, R (v. 4.2.0) and RStudio (v. 2022.07.1) were used. Data is presented as OR with 95% confidence intervals.

RESULTS

Patient characteristics

In total, 276 patients with breast cancer undergoing (neo-) adjuvant chemotherapy were included in the Phys-Can trial between March 2015 and April 2018. For this secondary analysis, 267 patients were selected. Reasons for not selecting patients: experimental treatment (n = 6), inclusion in another study (n = 1), stopped treatment without reason (n = 1), and diagnosis of metastatic breast cancer (n = 1). Baseline characteristics and treatment-related outcomes of included patients are presented in Table 1. Most prevalent co-morbid conditions included allergies (19%), high blood pressure (14%), sleep problems (13%) and anxiety (8%). Chemotherapy duration did not differ between patients receiving low or high dose chemotherapy or additional capecitabine treatment ($p > 0.050$). Patients started the baseline assessment period with a median of 10 days before the start of chemotherapy with no difference between patients receiving <85% or ≥85% of RDI ($p > 0.050$).

In total, 104 patients (39%) experienced dose adjustments (Supplementary Table 1). If the dose adjustment was caused by more than one reason, multiple side-effects were listed. Most patients received a combination of sequential taxane-based (docetaxel/paclitaxel) and anthracycline-based (epirubicin, cyclophosphamide) regimens with or without 5-fluorouracil. 13 patients (5%) received capecitabine in addition to standard regimens. 87 patients (32%) started chemotherapy with taxane-based and 167 (63%) patients with anthracycline-based regimens. Regardless of cycle order, most chemotherapy adjustments were performed in the taxane-based regimen

(Supplementary Table 1). For patients receiving additional capecitabine, 10 out of 13 (77%) patients experienced at least one dose-reduction.

Measures of inflammatory markers were available for 172 patients (64%). Reasons for not obtaining a sample included the loss to follow-up as for analysis of the main effect of exercise on inflammation [23], blood samples were only analyzed for participants with baseline and one additional measure [23]. Patients without available measures had a lower VO_2max ($p < 0.010$) and

differed in inclusion site ($p < 0.001$) and cancer stage ($p = 0.048$) while all other characteristics were similar ($p > 0.050$) to the analyzed group (Supplementary table 3).

Factors associated with low RDI

In total, 31 patients (12%) received an RDI of <85% (Table 2). A chemotherapy duration ≥20 weeks (p <0.001) and chemotherapy dose ($p = 0.006$) were significantly associated with a reduction in RDI in univariable analysis. Borderline effects were evident for inclusion site ($p = 0.069$) (Table 2).

In a multivariable analysis, a capecitabine addition (OR: 4.19; 95% CI: [0.97; 17.37]; $p = 0.048$) and a chemotherapy duration above 20 weeks (OR: 14.17 [3.99; 52.72]; $p < 0.001$) were associated with an RDI <85% (Figure 1). A sensitivity analysis including inclusion site did not change the results. Interestingly, infections (9% vs. 17%) and cardiovascular events (3% vs. 8%) occurred more frequently, whereas elevated liver values (9% vs. 2%) occurred less frequently in the <85% RDI group (Supplementary Table 2).

In total, 18 patients (11%) with available inflammatory data received an RDI of <85% (Figure 2a-e). IL-8 (OR: 1.61 [1.01; 2.58]; $p = 0.040$) and TNF-α (OR: 2.2 [1.17; 4.53]; $p = 0.019$), but not IL-6, CRP or IL-10 were associated with a reduction in RDI in univariable analyses (Figure 2g). For multivariable analyses (adjustment for age, BMI and chemotherapy dose), IL-8 (OR: 1.65 [0.99; 2.69]; $p = 0.044$) and TNF-α (OR: 2.95 [1.41; 7.19]; $p = 0.007$) were significantly associated with low RDI (Figure 2h; Supplementary table 4). Sensitivity analyses substituting CRP values below the detection limit with the detection limit divided by the square root of two did not yielded similar estimates.

Inflammation and chemotherapy-related dose adjustments

Exploratory analyses included the association of pre-chemotherapy inflammation and chemotherapy related side-effects leading to adjustments (Supplementary Table 5). Here, similar side-effects were combined, i.e. neurological (neuropathy, pain, hand-foot-syndrome) and gastroenterological

(nausea, vomiting, diarrhea) symptoms. In brief, a doubling of pre-chemotherapy TNF-α was associated with infections (OR: 2.62; [1.24; 6.82]; p = 0.022), cardiovascular (OR: 2.42 [0.98; 6.66]; p = 0.041) and gastroenterological (OR: 2.27 [1.08; 5.51]; p = 0.036) events. Notably, these associations were driven by a single data-point (non-extreme outlier; see methods section). For IL-6, a borderline association (OR: 1.51 [0.94; 2.41]; p = 0.071) was observed with infections (Supplementary Table 5).

DISCUSSION

In this analysis of 267 patients with breast cancer undergoing (neo-) adjuvant chemotherapy, we investigated factors associated with reduced RDI of chemotherapy. Both a chemotherapy duration ≥20 weeks and the chemotherapy regimen capecitabine were associated with an RDI <85%. Furthermore, pre-chemotherapy levels of IL-8 and TNF-α were significantly associated with an RDI <85% in univariable and multivariable analyses.

To our knowledge, this is the first report highlighting the association between pre-chemotherapy IL-8 and TNF-α and a reduction in RDI in women with early-stage breast cancer. This data expands previous knowledge on modifiable risk factors for chemotherapy completion rates in this population.

An RDI of ≥85% is associated with improve disease-free and overall survival [6]–[8] and the identification of risk factors for reduced RDI plays an important role in treatment administration. We did not find an association of patient characteristics, i.e. age, BMI, BSA, number of co-morbid conditions, aerobic fitness, cancer stage, receptor status or G-CSF administration with low RDI. Here, statistical power or selection bias of fitter patients due to the nature of the exercise intervention are likely. In contrast, a planned chemotherapy duration above 20 weeks was significantly associated with low RDI in our study which is in accordance with previous research [8]. Further, the addition of capecitabine to the standard treatment of selected patients with triple negative breast cancer [20] was associated with lower RDI in our analysis. This was likely caused by the increased overall chemotherapy dose of three instead of two chemotherapeutic regimens and the general toxicity of

capecitabine treatment [24].

Exercise concomitant to chemotherapy has been hypothesized to improve RDI [25, 26], but a recent systematic review found insufficient evidence to support this hypothesis due to methodological differences [27]. No difference was found for exercise intensity on RDI in the main analyses of the Phys-Can trial [28] and sensitivity analyses including exercise intensity data in this study did not reveal an association with RDI (data not shown).

As a novel part of the present study, we analyzed the influence of pre-chemotherapy inflammation on RDI in patients with available blood sample (n = 172). As the main reason for not obtaining an inflammatory measure was the loss to follow-up, the analysis likely includes fitter patients with lower cancer stage. To our knowledge, only one prior study has described the association between pre-treatment inflammation and RDI in patients with breast cancer. Yuan and colleagues reported that biological age, measured by IL-6 and the coagulation factor D-Dimer but not CRP was associated with reduced RDI (<85%) in 159 patients with early-stage breast cancer [18]. In contrast, IL-6 was not associated with RDI in our study. Participants included in this analysis were younger and had lower BMI. As plasma IL-6 increases with both age [29] and BMI [30], a higher IL-6 range was reported by Yuan and colleagues [18]. In addition, more <85% RDI observations (n = 36 vs. n = 18 in our study) occurred. Further, Yuan and colleagues found that increased age and decreased physical functioning were associated with a reduced RDI [18] while we found no association with age or fitness. Taken together, differences in the study population in combination with more <85% RDI observations might explain the observed difference for IL-6 compared to this study.

Interestingly, we found that high level of pre-chemotherapy IL-8 was associated with <85% RDI. In patients with metastatic prostate cancer, IL-8 has been associated with tumor load and post-relapse survival [14] and pre-chemotherapy IL-8 has been negatively associated with overall survival [31]. Taken together, IL-8 increases with cancer severity and lowers treatment response, hypothetically mediated by lower tolerability of chemotherapy. Another hypothesis entails an IL-8 mediated severity of chemotherapy-related side effects. Recently, IL-8 receptor inhibition has shown

to reduce chemotherapy-induced neuropathy in rodent models [32]. However, no connection between IL-8 and any type of chemotherapy adjustments was found in our study.

We further found that high systemic concentration of TNF-α was associated with low RDI. TNF-α blockade has been found to improve chemotherapy dose delivery and to decrease chemotherapy-related fatigue symptoms in 12 patients with advanced malignancies [33]. Here, we found pre-chemotherapy TNF-α to be associated with infections, gastroenterological and cardiovascular events but these observations were driven by a single patient exhibiting high TNF-α levels. Although the association between pre-chemotherapy inflammation and treatment-related side-effects remains speculative, there may be a mechanistic link of relevance to explore in future studies. Elevated pre-chemotherapy inflammation might cause ´immune cell exhaustion´ and it has been well described that e.g. exhausted T cells exhibit loss of effector functions [34]. Elevated and chronic exposure to TNF has been linked to T cell dysfunction [35] while tumor secreted IL-8 was found to impair natural killer cell function *in vitro* [36]. Further, obesity which is often linked to chronic low-grade inflammation was shown to drive both T and natural killer cell exhaustion [37], [38]. Although exploratory, patients with <85% RDI exhibited more infections leading to dose adjustments (17% vs. 9%), potentially driven by immune cell exhaustion. Exploring the relationship between inflammation and immune dysfunction, e.g. immune cell exhaustion in patients with cancer might help to understand the development and severity of infections during chemotherapy treatment. Here, high levels of pre-chemotherapy inflammation might lead to an immune system which is less responsive to new challenges such as chemotherapy, thereby leading to more infections or an increased infection severity during treatment.

Taken together, in contrast to IL-8 and TNF-α, common measures of systemic inflammation i.e., IL-6 or CRP, did not show an association with low RDI. As both IL-8 and TNF-α are potent immunomodulatory factors, an underlying dysfunction of the immune system might play a role in the occurrence of low RDI.

Data generated in this study might help to understand why patients experience

chemotherapy dose reductions. Inflammatory markers are easy and fast to measure and would provide additional information for oncologists to identify patients at risk. To date, day-to-day fluctuations and the lack of reference values for inflammatory markers in patients with cancer limits the translation across different populations. Therefore, larger trials including healthy controls need to determine cut-off values for single cytokines and combinations of cytokines to limit the influence of day-to-day fluctuations. In turn, inflammatory measures can then be used as addition to prognostic scores determining the risk of treatment adjustments.

If pre-treatment inflammation can be linked to specific toxicities occurring during chemotherapy, early signs can be recognized and treated without the need of chemotherapy dose reductions. Although cytokine receptor blockade has the potential to lower the inflammatory burden, some chemotherapeutic agents rely on the immune system [39] which might be impaired following a receptor blockade [40]. Alternatively, we have recently shown that high intensity exercise potentially decreases the accumulation of inflammatory markers during ongoing treatment [23].

In conclusion, the present study shows that elevated pre-chemotherapy levels of IL-8 and TNF-α were associated with low RDI. Previous research has linked both IL-8 and TNF-α to chemotherapy-related side-effects. Future studies should investigate the intriguing link between pre-chemotherapy inflammation and side-effect severity or immune cell exhaustion during treatment. Further, IL-8 and TNF-α could potentially provide new and modifiable risk factors to identify patients at risk for experiencing dose reductions.

Limitations:

Due to few observations of patients receiving <85% RDI multivariable adjustments are limited. Included patients are likely fitter and with a lower inflammatory burden compared to patients observed in clinical practice e.g., we included only few patients with stage III breast cancer. Further, no information regarding the time between surgery and initiation of adjuvant treatment was available. Treatment dosing was based on BSA and could be improved by inclusion of lean and

adipose tissue mass in future trials. Analyses surrounding CRP have to be interpreted cautiously, as different detection limits across study sites were present. Finally, chemotherapy-related side-effects were not graded based on the Common Terminology Criteria for Adverse Events (CTCAE) scale, limiting the interpretation of presented results.

REFERENCES

[1] Early Breast Cancer Trialists' Collaborative Group, "Effects of Adjuvant Tamoxifen and of Cytotoxic Therapy on Mortality in Early Breast Cancer," *N. Engl. J. Med.*, vol. 319, no. 26, pp. 1681–1692, Dec. 1988, doi: 10.1056/NEJM198812293192601.

[2] Early Breast Cancer Trialists` Collaborative Group, "Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100 000 women in 123 randomised trials," *Lancet*, vol. 379, no. 9814, pp. 432–444, 2012, doi: 10.1016/S0140-6736(11)61625-5.

[3] Early Breast Cancer Trialists' Collaborative Group, "Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials," *Lancet*, vol. 393, no. 10179, pp. 1440–1452, 2019, doi: 10.1016/S0140-6736(18)33137-4.

[4] W. C. Wood *et al.*, "Dose and Dose Intensity of Adjuvant Chemotherapy for Stage II, Node-Positive Breast Carcinoma," *N. Engl. J. Med.*, vol. 330, no. 18, pp. 1253–1259, May 1994, doi: 10.1056/NEJM199405053301801.

[5] M. J. Piccart, L. Biganzoli, and A. Di Leo, "The impact of chemotherapy dose density and dose intensity on breast cancer outcome: what have we learned?," *Eur. J. Cancer*, vol. 36, no. SUPPL. 1, pp. 4–10, 2000, doi: 10.1016/S0959-8049(99)00256-7.

[6] G. Bonadonna and P. Valagussa, "Dose-Response effect of adjuvant Chemotherapy in breast cancer," *N. Engl. J. Med.*, vol. 304, no. 1, pp. 10–15, 1981, doi: 10.1056/NEJM199401273300403.

[7] G. Bonadonna, P. Valagussa, A. Moliterni, M. Zambetti, and C. Brambilla, "Adjuvant Cyclophosphamide, Methotrexate, and Fluorouracil in Node-Positive Breast Cancer — The Results of 20 Years of Follow-up," *N. Engl. J. Med.*, vol. 332, no. 14, pp. 901–906, Apr. 1995, doi: 10.1056/NEJM199504063321401.

[8] M. Shayne, J. Crawford, D. C. Dale, E. Culakova, and G. H. Lyman, “Predictors of reduced dose intensity in patients with early-stage breast cancer receiving adjuvant chemotherapy,” *Breast Cancer Res. Treat.*, vol. 100, no. 3, pp. 255–262, 2006, doi: 10.1007/s10549-006-9254-4.

[9] G. H. Lyman, “Impact of chemotherapy dose intensity on cancer patient outcomes,” *J. Natl. Compr. Cancer Netw.*, vol. 7, no. 1, pp. 99–108, 2009, doi: 10.6004/jnccn.2009.0009.

[10] G. H. Lyman, D. C. Dale, D. Tomita, S. Whittaker, and J. Crawford, “A retrospective evaluation of chemotherapy dose intensity and supportive care for early-stage breast cancer in a curative setting,” *Breast Cancer Res. Treat.*, vol. 139, no. 3, pp. 863–872, 2013, doi: 10.1007/s10549-013-2582-2.

[11] D. Weycker, R. Barron, J. Edelsberg, A. Kartashov, and G. H. Lyman, “Incidence of reduced chemotherapy relative dose intensity among women with early stage breast cancer in US clinical practice,” *Breast Cancer Res Treat*, vol. 133, pp. 301–310, 2012, doi: 10.1007/s10549-011-1949-5.

[12] A. Mantovani, P. Allavena, A. Sica, and F. Balkwill, “Cancer-related inflammation,” *Nature*, vol. 454, no. 7203, pp. 436–444, 2008, doi: 10.1038/nature07205.

[13] G. J. Zhang and I. Adachi, “Serum interleukin-6 levels correlate to tumor progression and prognosis in metastatic breast carcinoma.,” *Anticancer Res.*, vol. 19, no. 2B, pp. 1427–1432, 1999.

[14] I. H. Benoy *et al.*, “Increased serum interleukin-8 in patients with early and metastatic breast cancer correlates with early dissemination and survival,” *Clin. Cancer Res.*, vol. 10, no. 21, pp. 7157–7162, 2004, doi: 10.1158/1078-0432.CCR-04-0812.

[15] R. Salgado *et al.*, “Circulating interleukin-6 predicts survival in patients with metastatic breast cancer,” *Int. J. Cancer*, vol. 103, no. 5, pp. 642–646, 2003, doi: 10.1002/ijc.10833.

[16] B. L. Pierce *et al.*, “Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients,” *J. Clin. Oncol.*, vol. 27, no. 21, pp. 3437–3444, 2009, doi:

10.1200/JCO.2008.18.9068.

[17] Y. A. Cho, M. K. Sung, J. Y. Yeon, J. Ro, and J. Kim, "Prognostic role of interleukin-6, interleukin-8, and leptin levels according to breast cancer subtype," *Cancer Res. Treat.*, vol. 45, no. 3, pp. 210–219, 2013, doi: 10.4143/crt.2013.45.3.210.

[18] Y. Yuan *et al.*, "Association of pre-chemotherapy peripheral blood pro-inflammatory and coagulation factors with reduced relative dose intensity in women with breast cancer," *Breast Cancer Res.*, vol. 19, no. 1, pp. 1–10, 2017, doi: 10.1186/s13058-017-0895-5.

[19] S. Berntsen *et al.*, "Design of a randomized controlled trial of physical training and cancer (Phys-Can) - the impact of exercise intensity on cancer related fatigue, quality of life and disease outcome," *BMC Cancer*, vol. 17, no. 1, pp. 1–12, 2017, doi: 10.1186/s12885-017-3197-5.

[20] H. Joensuu *et al.*, "Adjuvant capecitabine in combination with docetaxel, epirubicin, and cyclophosphamide for early breast cancer the randomized clinical finxx trial," *JAMA Oncol.*, vol. 3, no. 6, pp. 793–800, 2017, doi: 10.1001/jamaoncol.2016.6120.

[21] D. L. Longo, P. L. Duffey, V. T. DeVita, M. N. Wesley, S. M. Hubbard, and R. C. Young, "The calculation of actual or received dose intensity: A comparison of published methods," *J. Clin. Oncol.*, vol. 9, no. 11, pp. 2042–2051, 1991, doi: 10.1200/JCO.1991.9.11.2042.

[22] A. C. H. Bjørke, T. Raastad, and S. Berntsen, "Criteria for the determination of maximal oxygen uptake in patients newly diagnosed with cancer: Baseline data from the randomized controlled trial of physical training and cancer (Phys-Can)," *PLoS One*, vol. 15, pp. 1–18, 2020, doi: 10.1371/journal.pone.0234507.

[23] T. Schauer *et al.*, "Exercise intensity and markers of inflammation during and after (neo-) adjuvant cancer treatment," *Endocr. Relat. Cancer*, no. Accepted for publication, 2021, doi: http://dx.doi.org/10.1530/ERC-20-0507.

[24] C. Zielinski, J. Gralow, and M. Martin, "Optimising the dose of capecitabine in metastatic

breast cancer: Confused, clarified or confirmed?," *Ann. Oncol.*, vol. 21, no. 11, pp. 2145–2152, 2010, doi: 10.1093/annonc/mdq069.

[25] K. S. Courneya *et al.*, "Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial," *J. Clin. Oncol.*, vol. 25, no. 28, pp. 4396–4404, 2007, doi: 10.1200/JCO.2006.08.2024.

[26] H. van Waart *et al.*, "Effect of Low-Intensity Physical Activity and Moderate- to High-Intensity Physical Exercise During Adjuvant Chemotherapy on Physical Fitness, Fatigue, and Chemotherapy Completion Rates: Results of the PACES Randomized Clinical Trial.," *J. Clin. Oncol.*, vol. 33, no. 17, pp. 1918–1927, Jun. 2015, doi: 10.1200/JCO.2014.59.1081.

[27] K. A. Bland, K. Zadravec, T. Landry, S. Weller, L. Meyers, and K. L. Campbell, "Impact of exercise on chemotherapy completion rate: a systematic review of the evidence and recommendations for future exercise oncology research," *Crit. Rev. Oncol. / Hematol.*, vol. 136, pp. 79–85, 2019, doi: 10.1016/j.critrevonc.2019.02.005.

[28] I. Demmelmaier *et al.*, "Does exercise intensity matter for fatigue during (neo-)adjuvant cancer treatment? The Phys-Can randomised clinical trial," *Scand. J. Med. Sci. Sports*, vol. In Press, 2021, doi: 10.1111/sms.13930.

[29] M. Maggio, J. M. Guralnik, D. L. Longo, and L. Ferrucci, "Interleukin-6 in aging and chronic disease: A magnificent pathway," *Journals Gerontol. - Ser. A Biol. Sci. Med. Sci.*, vol. 61, no. 6, pp. 575–584, 2006, doi: 10.1093/gerona/61.6.575.

[30] C. P. Fischer, A. Berntsen, L. B. Perstrup, P. Eskildsen, and B. K. Pedersen, "Plasma levels of interleukin-6 and C-reactive protein are associated with physical inactivity independent of obesity," *Scand. J. Med. Sci. Sport.*, vol. 17, no. 5, pp. 580–587, 2007, doi: 10.1111/j.1600-0838.2006.00602.x.

[31] L. Tiainen *et al.*, "Low Plasma IL-8 Levels During Chemotherapy Are Predictive of Excellent Long-Term Survival in Metastatic Breast Cancer," *Clin. Breast Cancer*, vol. 19, no. 4, pp. e522–

e533, 2019, doi: 10.1016/j.clbc.2019.03.006.

[32] L. Brandolini *et al.*, "DF2726A, a new IL-8 signalling inhibitor, is able to counteract chemotherapy-induced neuropathic pain," *Sci. Rep.*, vol. 9, no. 1, pp. 1–12, 2019, doi: 10.1038/s41598-019-48231-z.

[33] J. P. Monk *et al.*, "Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-intensive chemotherapy in cancer patients," *J. Clin. Oncol.*, vol. 24, no. 12, pp. 1852–1859, 2006, doi: 10.1200/JCO.2005.04.2838.

[34] E. J. Wherry and M. Kurachi, "Molecular and cellular insights into T cell exhaustion," *Nat. Rev. Immunol.*, vol. 15, no. 8, pp. 486–499, 2015, doi: 10.1038/nri3862.

[35] M. Beyer *et al.*, "Tumor-necrosis factor impairs CD4+ T cell-mediated immunological control in chronic viral infection," *Nat. Immunol.*, vol. 17, no. 5, pp. 593–603, 2016, doi: 10.1038/ni.3399.

[36] J. Wu *et al.*, "IL-6 and IL-8 secreted by tumour cells impair the function of NK cells via the STAT3 pathway in oesophageal squamous cell carcinoma," *J. Exp. Clin. Cancer Res.*, vol. 38, no. 1, pp. 1–15, 2019, doi: 10.1186/s13046-019-1310-0.

[37] E. G. Aguilar and W. J. Murphy, "Obesity induced T cell dysfunction and implications for cancer immunotherapy," *Curr Opin Immunol*, vol. 51, no. 3, pp. 181–186, 2018, doi: doi:10.1016/j.coi.2018.03.012.

[38] I. Bähr, J. Spielmann, D. Quandt, and H. Kielstein, "Obesity-Associated Alterations of Natural Killer Cells and Immunosurveillance of Cancer," *Front. Immunol.*, vol. 11, no. March, 2020, doi: 10.3389/fimmu.2020.00245.

[39] L. Zitvogel, L. Apetoh, F. Ghiringhelli, and G. Kroemer, "Immunological aspects of cancer chemotherapy," *Nat. Rev. Immunol.*, vol. 8, no. 1, pp. 59–73, 2008, doi: 10.1038/nri2216.

[40] J. Clark, P. Vagenas, M. Panesar, and A. P. Cope, "What does tumour necrosis factor excess do to the immune system long term?," *Ann. Rheum. Dis.*, vol. 64, no. SUPPL. 4, pp. 70–76, 2005,

doi: 10.1136/ard.2005.042523.

Table 1: Patient and treatment-related factors of included participants

n	267
Age [years]; mean (SD)	53 (11)
BMI [kg/m^2]; mean (SD)	25 (5)
VO_2max [mL*kg^{-1}*min^{-1}]; mean (SD)	31 (7)
BSA [m^2]; mean (SD)	1.8 (0.2)
Chemotherapy duration [weeks]; median (range)	18 (9-27)
Site [n (%)]	
Uppsala	89 (33)
Lund	133 (50)
Linköping	45 (17)
Number of co-morbid conditions [n (%)]	
0	122 (46)
1	71 (27)
2	49 (18)
3+	17 (6)
Missing data	8 (3)
Cancer stage [n (%)]	
Stage I	111 (42)
Stage II	120 (45)
Stage III	16 (6)
Missing data	20 (7)
Receptor status [n (%)]	
ER+ and/or PR+, HER2-	142 (53)
HER2+	64 (24)
ER-, PR-, HER2- (triple negative)	36 (13)

Missing data	25 (10)
(Neo-) adjuvant setting [n (%)]	
Adjuvant	227 (85)
Neoadjuvant	40 (15)
Chemotherapy regimen [n (%)]	
F/E100C; Docetaxcel100	126 (47)
F/E75C; Docetaxcel75-80	82 (31)
F/E100C; Docetaxcel75-80	25 (9)
F/EC; Doc/Pac; Capecitabine	13 (5)
F/E100C; Paclitaxel	8 (3)
F/E75C; Docetaxcel100	5 (2)
F/E75C; Paclitaxel	5 (2)
Other	3 (1)

Abbreviations: BMI (body mass index), BSA (Body surface area), C (Cyclophosphamide), E (Epirubicin), ER (estrogen receptor), F (5-fluorouracil), HER2 (human epidermal growth factor receptor 2), PR (progesterone receptor), VO_2max (maximal oxygen consumption in mL/kg/min)

Table 2: Univariable analyses of patient and treatment-related factors associated with relative dose intensity

	RDI ≥85%	**RDI <85%**	**p-value**
n	236	31	
VO_2max [mL*kg^{-1}*min^{-1}]; mean (SD)	31 (7)	31 (7)	0.848
Age in years [n (%)]			0.983
<65	195 (83)	25 (81)	
≥65	41 (17)	6 (19)	
BMI in kg/m^2 [n (%)]			1.000
<25	141 (60)	19 (61)	
≥25	95 (40)	12 (39)	
Body surface area in m^2 [n (%)]			0.634
<2	216 (92)	27 (87)	
≥2	20 (8)	4 (13)	
Inclusion site [n (%)]			0.069
Uppsala	75 (32)	14 (45)	
Lund	117 (49)	16 (52)	
Linköping	44 (19)	1 (3)	
Number of co-morbid conditions [n (%)]			0.474
0	105 (44)	17 (55)	
1	65 (28)	6 (19)	
2	45 (19)	4 (13)	
3+	14 (6)	3 (10)	
Missing data	7 (3)	1 (3)	
Cancer stage [n (%)]			0.911

Stage I	100 (42)	11 (36)	
Stage II	109 (46)	11 (36)	
Stage III	14 (6)	2 (6)	
Missing data	13 (6)	7 (22)	
Receptor status [n (%)]			0.694
ER+ and/or PR+, HER2-	129 (55)	13 (42)	
HER2+	57 (24)	7 (23)	
ER-, PR-, HER2- (triple negative)	31 (13)	5 (16)	
Missing data	19 (8)	6 (19)	
G-CSF treatment [n (%)]			0.345
Yes	211 (89)	26 (84)	
No	15 (6)	4 (13)	
Missing data	10 (5)	1 (3)	
Chemotherapy setting [n (%)]			1.000
Adjuvant	201 (85)	26 (84)	
Neo-adjuvant	35 (15)	5 (16)	
Chemotherapy duration [n (%)]			<0.001
<20 weeks	230 (97)	24 (77)	
≥20 weeks	6 (3)	7 (23)	
Chemotherapy dose [n (%)][b]			0.006
Low dose	78 (33)	11 (36)	
High dose	149 (63)	15 (48)	
F/EC + Doc/Pac + Capecitabine	8 (3)	5 (16)	
Missing data	1 (1)	0	

Abbreviations: BMI (body mass index), ER (estrogen receptor), G-CSF (granulocyte colony stimulating factor), HER2 (human epidermal growth factor receptor 2), PR (progesterone receptor), RDI (relative dose intensity), VO_2max (maximal oxygen consumption in mL/kg/min); [a] Missing data not depicted; [b] High dose = if one or both

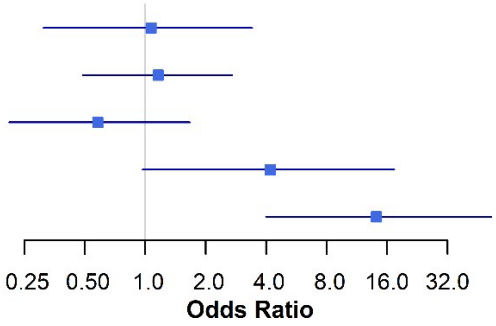
regimens contain either F/EC^{100} or Doc/Pac^{100}. Method: chi-square test of independence for categorical variables; Wilcoxon rank sum test for continuous variables.

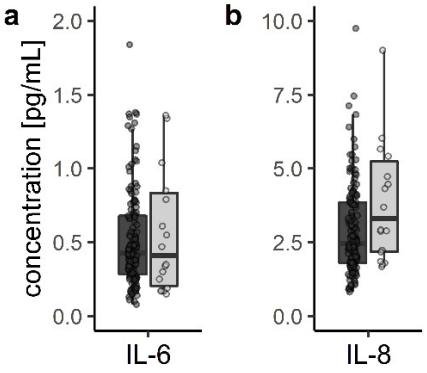
Figure Legends

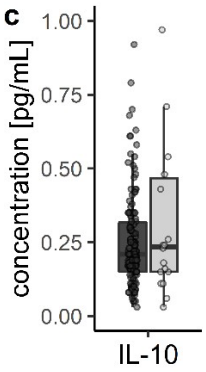
Fig. 1 Multivariable logistic regression of patient and treatment-related factors associated with RDI (n = 267) Reference: low dose chemotherapy; chemotherapy duration of less than 20 weeks. OR of 1.5 should be interpreted as 50% higher odds of having <85% RDI. *Abbreviations: BMI (body mass index), CI (confidence interval), OR (odds ratio), RDI (Relative dose intensity)*

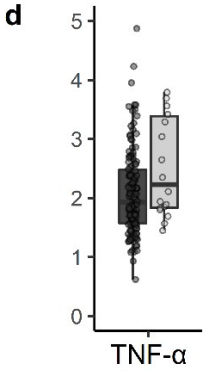
Fig. 2 Markers of inflammation and association with RDI (n = 172) Inflammatory markers (a) IL-6, (b) IL-8, (c) IL-10, (d) TNF-α, and (e) CRP for ≥85% RDI (dark boxes) and <85% RDI (light boxes). Data-points outside the axis are not shown but are included in boxplot statistics. (f) Concentration of measured inflammatory cytokines. Results of (g) univariable and (h) multivariable logistic regression. OR are based on doubling of the predictor cytokine. Multivariable models are adjusted for age, BMI, chemotherapy dose. Of note: data of RDI <85% includes one non-extreme outlier for TNF-α (see methods section). *As values for CRP below detection limit were treated as missing, different n apply (≥85% RDI: n = 91; <85% RDI: n = 14). *Abbreviations: CI (confidence interval), IL (Interleukin), OR (odds ratio), RDI (relative dose intensity), SD (standard deviation), TNF (Tumor necrosis factor)*

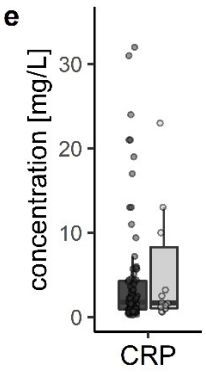
	OR (95% CI)	p-value
Age ≥65	1.07 [0.31; 3.41]	0.912
BMI ≥25	1.16 [0.49; 2.71]	0.736
Dose: high	0.58 [0.21; 1.67]	0.296
Dose: Capecitabine	4.19 [0.97; 17.37]	0.048
Duration: >20 weeks	14.17 [3.99; 52.72]	<0.001











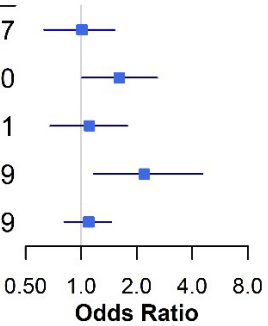
f

mean (SD)	≥85% (n=154)	<85% (n=18)	all
IL-6	0.77 (2.38)	0.66 (0.67)	0.76 (2.26)
IL-8	3.62 (6.8)	5.7 (8.56)	3.84 (7.01)
IL-10	0.28 (0.29)	0.34 (0.31)	0.29 (0.29)
TNF-α	2.21 (1.1)	4.77 (9.82)	2.48 (3.36)
CRP*	7.52 (25.43)	7.71 (13.02)	7.55 (24.1)

g

Univariable

	OR (95% CI)	p-value
IL-6	1.01 [0.63;1.52]	0.977
IL-8	1.61 [1.01;2.58]	0.040
IL-10	1.11 [0.68;1.78]	0.671
TNF-α	2.2 [1.17;4.53]	0.019
CRP*	1.1 [0.81;1.46]	0.509



h

Multivariable

	OR (95% CI)	p-value
IL-6	1.09 [0.67;1.66]	0.708
IL-8	1.67 [1.01;2.73]	0.037
IL-10	1.07 [0.64;1.77]	0.786
TNF-α	2.7 [1.34;6.01]	0.007
CRP*	1.14 [0.84;1.53]	0.366