Journal of Geriatric Oncology 9 (2018) 152–162

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

The effect of adjuvant chemotherapy on symptom burden and quality of life over time; a preliminary prospective observational study using individual data of patients aged ≥ 70 with early stage invasive breast cancer

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ARTICLE INFO

Article history:
Received 28 February 2017
Received in revised form 29 June 2017
Accepted 13 October 2017
Available online 20 November 2017

Keywords:
Breast cancer
Older cancer patients
Adjuvant chemotherapy
Geriatric assessment
Quality of life
Symptoms
Patient reports

ABSTRACT

Objectives: We aim to assess short and long term effects of chemotherapy on patient-reported quality of life (QOL) and patient versus clinician symptom reporting in older patients with breast cancer adjusted for tumour and aging parameters.
Material and Methods: In this prospective, multicentre, non-interventional, observational study, women aged ≥70 years were enrolled after surgery and assigned to a TC chemotherapy (docetaxel and cyclophosphamide) group or a control group depending on their planned adjuvant treatment. Longitudinal multivariate models were used to assess the statistical and minimal clinically important difference (MCID) in the impact of TC chemotherapy over time on QOL and symptom burden adjusted for baseline aging and tumour parameters. Statistical significance was set at 5% and MCID at 10 points.
Results: In total, 57 patients were enrolled in the chemotherapy and 52 patients in the control group. Within the chemotherapy group, clinical deterioration was reported at 3 months for Fatigue (17.73), Dyspnoea (17.05), Diarrhoea (12.06) and Appetite Loss (17.05) scores (all $p < 0.001$). However, the scores had returned to baseline (or even better for Role Functioning) at year 1. No clinical deterioration was reported in the control group. Symptom scores as reported by patients were significantly ($p < 0.05$) higher than those reported by the clinicians, even more so for Fatigue, Dyspnoea, and Pain.
Conclusion: Our results show that symptom burden and diminished QOL in an older breast cancer population receiving adjuvant TC chemotherapy are short-lived and disappear after a while with no long-term differences compared to a similar population not receiving chemotherapy.

1. Introduction

Breast cancer risk increases with age, with a third of female breast cancers currently diagnosed in patients older than 70. This number will most likely rise with an aging population [1]. Nowadays, breast cancer can be treated and currently adjuvant chemotherapy is the recommended option for high risk patients as it reduces the risk of distant recurrence [2] and mortality [3].

Unfortunately, older patients are often excluded from chemotherapy given clinicians' concerns about its toxic effects, including symptom burden and negative impact on their quality of life (QOL) [4–6]. Moreover, chemotherapy is expected to accelerate the aging process, making the

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https://doi.org/10.1016/j.jgo.2017.10.001
1879-4068/

already vulnerable older cancer population even more vulnerable. Whether this is the optimal treatment in this population remains unclear, as older patients tend to be underrepresented or excluded from clinical trials [7,8]. This leaves clinicians with little to no evidence on which to base their treatment decisions and potentially results in the 'under-treatment' of many older patients with breast cancer [9].

In this situation, when there is uncertainty regarding the risks and benefits of adjuvant chemotherapy, QOL and symptom reporting by patients can provide additional information for clinicians [10,11] because of its subjective nature [12], especially since older patients with cancer may themselves choose a better QOL above a prolonged life expectancy.

As little is known [13] about the effect of chemotherapy on older patients with breast cancer QOL, the primary goal of this observational study was to analyze the short and long term effect of adjuvant chemotherapy on patient-reported QOL and symptom burden using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). In addition, we wanted to control for frailty at entry of study in our analysis, given that aging is an individual process and varies considerably from person to person [14]. Frailty is defined as a consequence of age-related decline in many physiological systems, which collectively results in vulnerability to sudden health status changes triggered by minor stressor events [15]. The presence of frailty can be assessed using geriatric assessment (GA) [16,17], which is a systematic procedure to assess a patient's health status, focusing on the somatic, psychosocial, and functional domains [18], and which has been demonstrated to identify previously unrecognized health issues in older patients with cancer [19]. In addition to GA, we decided to assess several biological aging markers which are proposed in the literature to be correlated with the frailty of a patient [20] as they have the potential to reflect 'biological age' more accurately than clinical assessment [21].

As treatment-related symptoms are also reported by clinicians, and given the widely observed disagreement [10] between patient and clinician scoring, a secondary goal of this study was to compare patient versus clinician scores for a specific set of symptoms. Our results would then demonstrate how the effect of chemotherapy on the symptom burden is perceived differently (whether worse or better) by the patient versus clinician.

2. Methods

2.1. Patients and Data

This prospective, multicentre, non-interventional, observational study enrolled patients from two university and three regional hospitals in Belgium from 2009 to 2012. Eligible patients were women ≥ 70 years of age enrolled after surgery and assigned to either a chemotherapy group (CTG) or control group (CG) according to the adjuvant treatment they were to receive as decided upon by their physicians in accordance with international guidelines regarding risk factors [22]. A total of 109 patients were included in the study. Of these, 52 were enrolled in the CG, where they received an aromatase inhibitor. For the 57 patients in the CTG, the scheduled therapy consisted of docetaxel at a dose of 75 mg/m^2 and cyclophosphamide at 600 mg/m^2 every 3 weeks for a total of 4 cycles. Full details are reported elsewhere [23]. The study was approved by the Ethics Committees of the hospitals involved and written consent was provided by all participating patients.

There were three outcome measures: patient-reported symptoms and QOL, frailty as assessed by GA, and degree of aging as indicated by markers in blood samples. These three measures were taken at three time points: baseline (T0), defined as three to six weeks after surgery, but before first chemotherapy administration in the CTG group; approximately 3 months after inclusion (T1) (for CTG: day of last chemotherapy, but before chemotherapy was given); and around 1 year after inclusion (T2).

Patient-reported symptom burden and QOL were assessed using the EORTC QLQ-C30 questionnaire. The EORTC QLQ-C30 incorporates 15 parameters; one Global Health scale, five functioning scales (Physical, Role, Cognitive, Emotional and Social Functioning); three symptom scales (Fatigue, Pain, and Nausea and Vomiting), and seven single items (Dyspnoea, Appetite Loss, sleepiness, Constipation, Diarrhoea, and the perceived financial effect of disease and treatment) [24].

The geriatric screening and assessment (GA) was performed as recommended by the International Society of Geriatric Oncology (SIOG) [16,25] and described elsewhere [22]. It included the following geriatric assessment parameters: the Charlson Comorbidity Index (CCI) [26], Katz's Activities of Daily Living (ADL) [27], Lawton's instrumental Activities of Daily Living (iADL) [28], the Mini Mental State Examination (MMSE) [29] and the Mini Nutritional Assessment (MNA) [30]. Additionally, two summary scales were included, the Balducci frailty criteria [31] and Leuven Oncogeriatric Frailty Score (LOFS) [20]. Physicians also completed the G8, which consists of 7 items from the MNA questionnaire and the patient's age.

Blood was sampled in 4-mL EDTA K2E tubes for plasma isolation and leukocyte DNA extraction. Mean leukocyte telomere length (LTL) was measured on leukocyte DNA by qPCR and plasma levels of interleukin 6 (IL-6), interleukin 10 (IL-10), insulin-like growth factor 1 (IGF-1), tumour necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1) and regulated on activation, normal T cell expressed and secreted (RANTES) were assessed by means of ELISA.

As noted above, patient scoring of symptoms was also compared with physician scoring. This was done at T1 and T2 for five symptoms, Diarrhoea, Nausea and Vomiting, Fatigue, Dyspnoea and Pain. While patients reported their symptoms using the EORTC QLQ-C30, physicians used the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4 (NCI-CTCAE v4), as a standard classification system for reporting adverse events in cancer clinical trials [32].

The scoring systems used in these instruments are not identical. In the EORTC QLQ-C30 questionnaire, a score of 1 means "not at all", 2 means "a little", 3 means "quite a bit" and4 means "very much". By contrast, in the NCI-CTCAE scoring, a score of 0 means "none to normal", 1 means "mild", 2 means "moderate", 3 means "severe," and 4 means "life threatening or disabling". We therefore matched the scoring systems as follows: EORTC QLQ-C30 score 1 = NCI-CTCAE score 0; EORTC QLQ-C30 score 2 = NCI-CTCAE score 1; EORTC QLQ-C30 score 3 = NCI-CTCAE score 2; EORTC QLQ-C30 score 4 = NCI-CTCAE scores 3 and 4 combined.

2.2. Statistical Analysis

Unadjusted mean scores and 95% confidence intervals (CI) were calculated for the 15 EORTC QLQ-C30 scores at each time point for both the experimental group (CTG) and the control group (CG).

To assess short (from T0 to T1) and longer (from T0 to T2) term effects of TC chemotherapy on patients' QOL and symptom reporting we used longitudinal multivariate models including an interaction between time and treatment to assess between treatment differences in longitudinal changes corrected for baseline frailty, defined by chronological age and biological and clinical aging parameters and tumour characteristics Tumour (TNM classification 1 versus 2), pathological Nodes (TNM classification 0 versus 1–3) and Breast Cancer Phenotype.

The model selection was performed in two steps. First, in the univariate model, each tumour and frailty parameter was independently assessed with a criterion of $p < 0.05$. Second, the list of statistically significant frailty parameters from the univariate model was