Breast Cancer Res Treat (2012) 136:789–794
DOI 10.1007/s10549-012-2311-2

CLINICAL TRIAL

Influence of age, performance status, cancer activity, and IL-6 on anxiety and depression in patients with metastatic breast cancer

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Received: 29 August 2012 / Accepted: 19 October 2012 / Published online: 3 November 2012

Abstract Depression and anxiety are the core disorders causing emotional distress in patients (pts) with metastatic breast cancer. The aim of our study was to screen metastatic breast cancer outpatients for anxiety and depression, and to investigate the influence of age, Karnofsky Performance Status (KPS), cancer activity, and inflammation as represented by IL-6 levels on these two mood disorders. Pts treated with chemotherapy for metastatic breast cancer ($n = 70$) were assessed using the Hospital Anxiety and Depression Scale (HADS) for symptoms (scores 0–21) and caseness (score $\geq$11) of clinical depression and anxiety. Blood samples for IL-6 concentrations were collected at 10:00 a.m. A total of 22 (31.4 %) pts were diagnosed with caseness of clinical depression and 23 (32.9 %) pts with clinical anxiety, while 12 pts were diagnosed positive for both mood disorders. Depression and anxiety were positively but moderately correlated (Spearman's $r^2 = 0.24$, $p < 0.001$). IL-6 was significantly correlated with symptoms of depression ($r^2 = 0.42$, $p < 0.001$) and to a lesser extent to symptoms of anxiety ($r^2 = 0.16$, $p = 0.001$). In addition, IL-6 was positively associated with tumor progression ($p < 0.001$). Multiple linear regression analysis showed that tumor progression (standardized $b = 0.226$, $p = 0.047$), symptoms of anxiety ($b = 0.292$, $p = 0.016$), and IL-6 ($b = 0.314$, $p = 0.007$) were independently associated with clinical depression, whereas anxiety was linked to tumor progression ($b = 0.238$, $p = 0.030$), symptoms of depression ($b = 0.407$, $p < 0.001$) and age ($b = -0.381$, $p < 0.001$), but not to IL-6 ($b = 0.168$, $p = 0.134$). Even though a positive correlation between depression and anxiety exists, clinical parameters like age, cancer activity, KPS, and IL-6 do influence depression and anxiety differently. Unlike clinical depression, anxiety is not associated with increased IL-6 levels, however, shows a reciprocal correlation with age.

Keywords Metastatic breast cancer · Anxiety · Depression · Interleukin 6 · Karnofsky performance status

Abbreviations

DSM-IV	Diagnostic and statistical manual of mental disorders
HADS	Hospital Anxiety and Depression Scale

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IL-6	Interleukin 6
KPS	Karnofsky performance status
MMSE	Mini-mental state examination
PD	Progressive disease
PR	Partial remission
Pts	Patients
SD	Stable disease
WHO	World Health Organization

Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23 % of the total cancer cases and 14 % of the cancer deaths [1]. The great majority of these deaths are due to recurrent metastatic disease. Systemic therapy whether hormonal treatment or cytotoxic chemotherapy is often administered in the outpatient setting implying that most women must manage cancer symptoms and treatment-associated side effects alone at home without their oncologists having a closer eye on them. Thus, physicians tend to underestimate the degree of emotional distress experienced by their patients in this life-threatening situation. Depression and anxiety are the core disorders causing emotional distress in cancer patients. Early recognition and treatment of these two disorders can not only improve the quality of life of cancer patients but also may prolong survival and compliance with chemotherapy [2–5].

Anxiety is an emotional state dominated by feelings of tension, nervousness, fear, and worry and symptoms of autonomic nervous system over-activity. These include high blood pressure, palpitation or tremor, and irregular breathing. Anxiety is a response to a threat, and cancer is a real threat. One could almost forsake anxiety as being an understandable reaction in this situation. However, abnormal anxiety can be disruptive and have great negative impact on quality of life. Recognizing disruptive anxiety is an obviously not clear cut task in metastatic breast cancer patients. This is illustrated by the wide range of prevalence estimates of abnormal anxiety in cancer. They vary from 1 to 71 % [6, 7].

In addition to anxiety, a significant portion of patients develop a depressive disorder ranging from a mild depressive mood to major depression as defined by diagnostic and statistical manual of mental disorders (DSM-IV) criteria [8]. It is important in this context to distinguish between understandable feelings of sadness and grief brought about by a painful life experience such as the diagnosis of cancer on one side, and clinical depression which requires sufficient recognition and treatment on the other side. The incidence of depression in cancer patients is comparable to that seen in hospitalized patients with other serious medical conditions [9]. A number of studies have examined the prevalence of depression among patients with breast cancer and found rates ranging from 10 to 55 % [10]. To complicate things further, studies have shown a high correlation between depression and anxiety in patients with cancer [11, 12].

The concept of sickness behavior, a syndrome that shares many characteristics with depression and includes symptoms of anxiety, has lead to the speculation that pro-inflammatory cytokines might also play a role in depression and anxiety [13–15]. Several studies have shown a significant association of cytokines, especially.

IL-6, with depression in patients with and without cancer [16, 17]. Given the relevance of anxiety and depression for clinical outcome and quality of life in cancer patients, a better understanding of the relationship between these two mood disorders and of the influence of age, Karnofsky Performance Status (KPS), cancer activity, and markers of inflammation like IL-6 on depression and anxiety is necessary.

Patients and methods

In this cross-sectional study, 70 patients currently receiving systemic chemotherapy for advanced metastatic breast cancer in the outpatient setting were assessed for symptoms of depression and anxiety. Patient characteristics like age, KPS [18], number and location of metastatic sites, adjuvant treatment, palliative chemotherapy, and receptor status were recorded. In addition, cancer activity as evaluated within the last 4 weeks was documented [progressive disease (PD) vs. stable disease (SD) or partial remission (PR) according to RECIST criteria, Version 1.1] [19]. Patients were either receiving their current course of chemotherapy or starting a new line of chemotherapy, due to progression. Various chemotherapies were applied, according to clinical condition of the patient, HER-2 receptor status and approval status of the drugs at the time. This investigation was approved by the institutional ethics committee, all patients gave their written informed consent.

All subjects presented themselves with a mini-mental state examination score of at least 24 [20]. Exclusion criteria were as follows: radiation therapy within the last 3 months, untreated endocrine diseases, renal insufficiency requiring dialysis, or any form of neurological malfunction, i.e., meningeosis carcinomatosa or brain metastases. None of the patients were receiving antidepressant agents, anticonvulsives, or other psychotropic medication for treatment of affective disorders. Exclusion criteria also included current evidence of substance/alcohol abuse, known diagnosis of affective disorders (even if untreated), long-term steroid use (>8 weeks).

To measure symptom level of depression and anxiety, all participants completed the Hospital Anxiety (HADS-A), and Depression Scale (HADS-D) on the same day as the IL-6

draw before receiving chemotherapy. The HADS is a well-validated self-rated fourteen-item scale, developed specifically for the assessment of depressive symptoms in medically ill patients [21, 22]. Scores ≥11 (threshold score) on either the depression or the anxiety scale (scale range 0–21) are considered to indicate a probable diagnosis of clinical depression or anxiety in patients with somatic disease [23]. All those patients with a probable caseness of clinical depression and anxiety were further examined with a structured clinical interview according to the criteria of the DSM-IV [24].

Blood samples for the measurement of IL-6 concentrations were collected at 10:00 a.m., before administration of chemotherapy, by venipuncture into EDTA tubes, placed on ice, centrifuged for acquisition of plasma, and stored at −80 °C for subsequent testing [25]. Plasma IL-6 levels were measured with commercially available kits following the manufacturer's protocol (Immulite/Immulite 1000 IL-6, DPC Biermann, Germany). Samples were assayed in duplicate, and IL-6 concentrations were derived from a standard curve established from serial dilutions (2–625 pg/ml) of recombinant human IL-6. Assay sensitivity was <2 pg/ml. The mean inter- and intra-assay coefficients of variation were 10.9 and 3.6 %, respectively. All samples were assayed by personnel who were blind to the identity of the study subjects.

Statistical methods

Descriptive analysis included absolute and relative frequencies for categorical variables, as well as mean, standard deviation, median, and range for numerical measurements. For univariate group comparisons, the χ^2 test and the *t* test or, in case the normal distribution assumption being violated, the Mann–Whitney's *U*test were performed. Correlations were evaluated using the Spearman's correlation coefficient. In order to measure the concordance between clinical depression and anxiety, Cohen's kappa was used. All results were considered significant at $p < 0.05$ (two-tailed). Independent predictors for depression and anxiety were identified using multiple linear regression analysis with depression or anxiety as the dependent variable, and age, IL-6, cancer status, KPS score, and HADS-A score (or HADS-D score, respectively) as the independent variables. The resulting models were obtained after forward and backward selection. For comparability, standardized regression coefficients are presented as well.

Results

A total of 70 patients with metastatic breast cancer receiving chemotherapy in the outpatient clinic were screened for symptoms of depression and anxiety. The demographic characteristics of these patients are displayed in Table 1. The average age of the participants was 59.9 years (SD 10.2 years). Patients presented themselves with a moderate KPS (median 65 %). Table 2 demonstrates the proportion of outpatients with normal, borderline, and abnormal scores for depression and anxiety subscales. 22 (31.4 %) patients showed a depression subscale score of 11 or more and therefore presented a probable case of clinical depression. On the other hand, 23 (32.9 %) patients showed a score of 11 or more on the anxiety subscale and therefore presented a probable case of anxiety with an overlap of 12 patients showing abnormal scores on both the depression and anxiety subscales, indicating concurrent caseness of clinical depression and anxiety. All patients showing caseness of clinical depression and/or anxiety showed a pattern of symptoms that satisfied the DSM-IV criteria. Symptoms of depression and anxiety were positively but moderately correlated (Spearman's $r^2 = 0.24$, $p < 0.001$) (Fig. 1). A comparable result was obtained for the concordance between caseness of clinical depression and anxiety (Cohen's kappa = 0.312, $p = 0.014$).

42 (60 %) of the patients had PD whereas 22 (31.4 %) were classified as having SD at the time of study inclusion. Only 6 (8.6 %) of the patients were in PR at the time of their previous tumor staging (≤4 weeks ago). The presence of depression was dependent on cancer activity (i.e., progressive disease ($\chi^2 = 9.1$; degrees of freedom (df) = 1; $p = 0.003$), the same was true for anxiety, however, to a lesser extent ($\chi^2 = 6.6$; df = 1; $p = 0.011$). IL-6 was strongly correlated with the severity of symptoms of depression ($r^2 = 0.65$, $p < 0.001$; Fig. 2) and disease status (PD vs. SD + PR) ($p < 0.001$; Table 3) and to a lesser extent to the symptoms of anxiety ($r^2 = 0.40$, $p = 0.001$; Fig. 2). However, when looking at clinical manifestations of depression and anxiety, only depression versus no depression showed a significant difference in IL-6 levels (20 pg/ml [1–199] versus 2.8 pg/ml [0–101]; $p < 0.001$; Table 4).

Confirmatory analysis concerning independent predictors for depression and anxiety showed that after multiple linear regression analyses with both, forward and backward selection, cancer activity (standardized $b = 0.226$, $p = 0.047$), symptoms of anxiety ($b = 0.292$, $p = 0.016$), and IL-6 ($b = 0.314$, $p = 0.007$) were independently associated with depression, whereas anxiety is predicted by cancer activity ($b = 0.238$, $p = 0.030$), symptoms of depression ($b = 0.407$, $p < 0.001$), and age ($b = -0.381$, $p < 0.001$). Anxiety showed a significant reciprocal correlation with age ($r^2 = 0.39$, $p = 0.001$; Fig. 3).

Discussion

About one-third of the patients investigated were diagnosed with clinical depression or anxiety. This confirms

Table 1 Demographic and clinical characteristics of 70 patients with advanced metastatic breast cancer

Variable	Women with metastatic breast cancer
Mean age (SD)	59.9 (10.2) years
Karnofsky performance status	65 %
Previous adjuvant treatment *n* (% of patients)	
Chemotherapy	53 (75 %)
Endocrine therapy	17 (25 %)
Number of metastatic sites	
1	13 (18.6 %)
2	24 (34.3 %)
>2	33 (47.1 %)
Median number of metastatic sites	2 (1–5)
Metastatic sites *n* (% of patients)	
Visceral metastases	66 (94.3 %)
Lung	29 (41.4 %)
Liver	55 (78.6 %)
Bone	48 (68.6 %)
Soft tissue	21 (30 %)
Hormone receptor status (%)	
Positive	43 (61.4 %)
Negative	20 (28.6 %)
Unknown	7 (10 %)

Table 2 Scores on the HADS subscales for 70 metastatic breast cancer patients; anxiety scale HADS-A (range 0–21), and depression scale HADS-D (range 0–21)

Status	Score results		
	Normal (0–7)	Borderline (8–10)	Caseness (11–21)
HADS-A (anxiety scale)	34 (48.6 %)	13 (18.6 %)	23 (32.9 %)
HADS-D (depression scale)	41 (58.6 %)	7 (10 %)	22 (31.4 %)

prior reports in metastatic cancer patients [27]. All of these patients were referred to adequate supportive services and received either pharmacological or non-pharmacological intervention.

The gold standard used for diagnosis of depression and anxiety in somatic healthy patients, as defined by the DSM-IV diagnostic criteria, is difficult to apply in cancer patients. Most of these questionnaires and rating scales used for psychiatric screening and diagnosis are difficult to interpret in cancer patients because they include somatic symptoms that very often may be attributed to tumor symptoms or side effects of chemotherapy. The advantages of the HADS are that it makes no reference to somatic

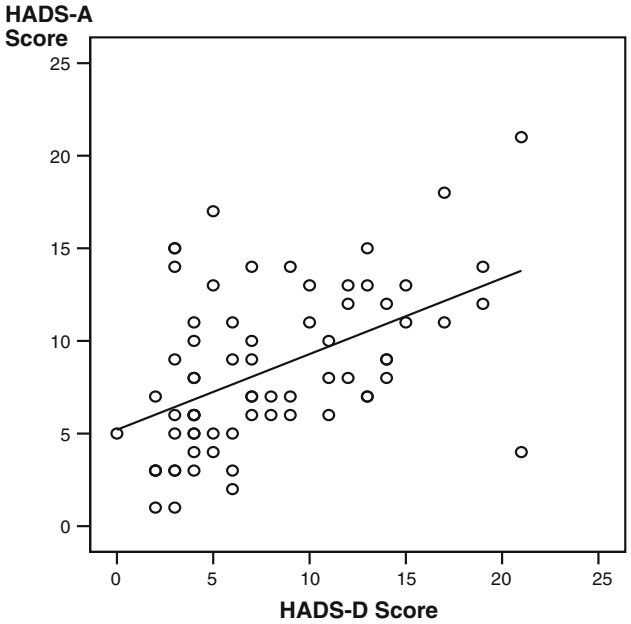

Fig. 1 Correlation between symptoms of anxiety and depression as measured by HADS-A and HADS-D in $n = 70$ patients with advanced metastatic breast cancer ($r = 0.24$, $p = 0.001$)

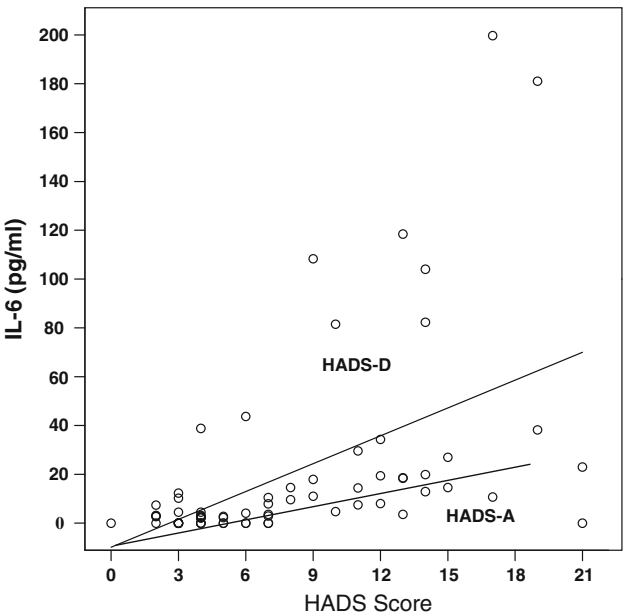

Fig. 2 Correlation of IL-6 concentrations (pg/ml) and level of depression (HADS-D; $r = 0.651$, $p < 0.001$) as well as level of anxiety (HADS-A; $r = 0.401$, $p = 0.01$) in $n = 70$ patients with advanced metastatic breast cancer

symptoms and is well evaluated to detect caseness of depression and anxiety disorder in cancer patients [23].

The intention of this study was to investigate the influence of age, cancer activity (progression or remission), KPS and inflammatory markers such as IL-6 on depression and anxiety, in addition to understanding the interaction

Table 3 Differences (median) of IL-6 levels, HADS-A and HADS-D scores according to cancer activity (SD + PR vs. PD)

Parameter	Cancer activity			
	SD, PR (n = 28)	vs.	PD (n = 42)	U test
IL-6 (pg/ml)	2.3 (0–8)	vs.	12.9 (0–179)	$p < 0.001$
HADS-A anxiety scale (range 0–21)	6 (3–13)	vs.	9 (0–21)	$p = 0.001$
HADS-D depression scale (range 0–21)	4 (2–12)	vs.	9 (1–21)	$p = 0.001$

Table 4 Median IL-6, age, and KPS values for depression versus no depression and anxiety versus no anxiety

Parameter	Depression (n = 22)	vs.	No depression (n = 48)	U test	Anxiety (n = 23)	vs.	No anxiety (n = 47)	U test
IL-6 (pg/ml)	20 (1–199)	vs.	2.8 (0–101)	$p < 0.001$	11.7 (2–199)	vs.	3.2 (1–104)	$p = 0.41$
Age	60.5 (46–85)	vs.	59 (40–81)	$p = 0.48$	52 (40–85)	vs.	61 (44–83)	$p = 0.02$
KPS	65 (40–90)	vs.	70 (30–90)	$p = 0.71$	70 (30–80)	vs.	60 (40–90)	$p = 0.51$

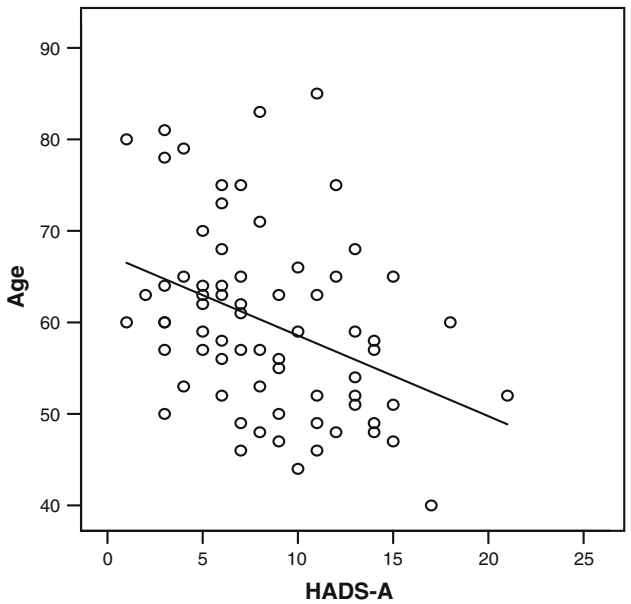

Fig. 3 Correlation between age symptoms of anxiety, measured by HADS-A in $n = 70$ patients with advanced metastatic breast cancer ($r = 0.39$, $p = 0.001$); r = Spearman rank order (ρ)

between these two disorders. This study tried to compile a significantly large and homogenous sample of patients, concerning confounding factors, such as age, medication, performance status and outpatient treatment. All patients had advanced metastatic (stage IV) breast cancer and were receiving chemotherapy as outpatients.

IL-6 was strongly correlated with the severity of symptoms of depression, cancer activity (progressive disease) and to a lesser extent to the symptoms of anxiety. However, when looking at clinical manifestations of these affective disorders, IL-6 only had a negative influence on clinical depression.

High levels of inflammatory markers, such as IL-6, have previously been linked to progression of metastatic breast cancer and to a poor prognosis [28–30]. The underlying mechanisms possibly include an IL-6-induced alteration of tumor cell biology and activation of stromal cells, facilitating tumor growth and metastasis [31, 32]. Different sets of predictors for depression and anxiety have been identified. While clinical depression is independently and positively associated with cancer activity, symptoms of anxiety and IL-6, clinical anxiety on the other hand positively depends on cancer activity, symptoms of depression and age, but not on IL-6. Instead, there is a reciprocal association between age and anxiety. KPS had no influence on depression or anxiety.

The influence of IL-6 on depression has been shown extensively and mechanisms induced through inflammation have been postulated [14]. Interestingly, IL-6 seems to have no influence on anxiety, even though symptoms of depression and anxiety are correlated. Disease activity (progressive disease) seems to have affected anxiety by other means than inflammation. In addition, life experience, indicated by older age, is associated with less anxiety. Noyes et al. [26] showed that young adults with cancer experienced greater anxiety and distress than older patients, possibly due to the effect of cancer on life plans. One of the limitations of these results is that pain evaluations were omitted. Although none of the patients were in eminent pain, a high percentage of cancer patients were, however, under chronic pain medication including nonsteroidal anti-inflammatory drugs. So far, the role of pain in the pathophysiology of depression and anxiety remains unclear. In addition, other possible confounding factors like adiposity, social economic status, and smoking were not accounted for. The confounding influence of these factors on inflammation, tumor progression, and distress remains unclear [33–35].

There was a positive correlation between depression and anxiety in our study. The relationship between these two disorders is difficult to define in patients with cancer. Other

studies have shown high correlations between depression and anxiety and have suggested a single, broader underlying construct [12]. In conclusion, our findings suggest that there are two different populations with different characteristics, however, with possible overlaps. Cancer status, KPS, age, and IL-6 had varying and distinct influence on clinical depression and anxiety. Given the relevance of anxiety and depression to clinical outcome and quality of life, a better understanding of the relationship between these two disorders and markers of inflammation like IL-6 can be helpful adjuncts in diagnostic assessment, monitoring, and therapeutic intervention.

Conflict of interest None.

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