Cytokine 104 (2018) 72–77

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Elevated serum levels of proinflammatory cytokines potentially correlate with depression and anxiety in colorectal cancer patients in different stages of the antitumor therapy

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ARTICLE INFO

Keywords:
Cytokines
Anxiety
Depression
Colorectal cancer

ABSTRACT

Depression and anxiety, the most important psychological disorders in cancer patients, have now been considered as psychoneuroimmunological disorders, in which peripheral immune activation, through the release of proinflammatory cytokines, is implicated in the variety of behavioral, neuroendocrine and neurochemical alterations associated with these disorders. Along with the tumor itself, cancer treatment can also contribute to exacerbate the production of proinflammatory cytokines. This study aimed to investigate whether proinflammatory cytokine levels are related to depression and anxiety in CRC patients in different stages of the antitumor therapy We evaluated 60 patients in three stages of antitumor therapy (Pre-chemotherapy, Under-chemotherapy and Post-chemotherapy, n = 20 in each group) and 20 healthy volunteers by the Hospital Anxiety and Depression Scale (HADS). Serum levels of cytokines were measured by CBA. Depression and/or anxiety were found at clinically relevant levels in CRC patients during all antitumor therapy. Patients in pre-chemotherapy group exhibited the highest concentrations of pro-inflammatory cytokines and the lowest levels of IL-10. In latter stages of treatment, cytokines reached levels similar to the control group. Correlation analysis between HADS score and cytokine serum levels revealed positive associations of anxiety and/or depression with IL-1β, IL-6, IL-8, and TNF-α, and a negative correlation with IL-10, suggesting that cytokines are involved in the pathophysiology of these psychological disorders in CRC patients. A better understanding of the molecular mechanisms involved in these psychological disorders will allow the design of new therapeutic strategies to assist in alleviating such symptoms in cancer patients.

1. Introduction

Although the advances in chemotherapy at recent decades, colorectal cancer (CRC) is still the third most frequent cancer and the fourth deadliest in the world [1]. In Brazil, National Cancer Institute estimated that in 2016, approximately 18,000 women would be affected by CRC, surpassing for the first time the number of cases of cervical cancer, trailing only breast tumors. Among men, 17,000 new cases were estimated, a number surpassed only by lung and prostate tumors [2].

Cancer patients suffer from high emotional distress and experience a variety of affective states, including depression and anxiety, which are considered the most important psychological disorders in these individuals [3–5]. These symptoms closely interact with biologic stressors such as pain and physical symptom burden [6], usually affecting cancer progression, survival, and patient's quality of life [7,8]. Thus, the identification and proper management of these disorders is an important issue in oncology practice [9].

In addition to the obvious emotional and psychosocial dimensions of depression in cancer, evidence suggests that biological mechanisms may also be important [10]. Depression and anxiety have now been considered as psychoneuroimmunological disorders, in which peripheral immune activation, through the release of proinflammatory cytokines, is implicated in the variety of behavioral, neuroendocrine and neurochemical alterations associated with these psychological disorders

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http://dx.doi.org/10.1016/j.cyto.2017.09.030
Received 26 December 2016; Received in revised form 28 August 2017; Accepted 25 September 2017
Available online 29 September 2017
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[11,12]. The demonstration of a possible contribution of the immune system to the development of depression is likely to open new avenues in psychopathology.

Besides being strongly associated with depression, inflammation plays crucial roles in all stages of tumor development [13]. In tumor microenvironment, cells like infiltrated inflammatory cells, endothelial cells, tumor-associated fibroblasts and, mostly, epithelial cells including tumor cells produce proinflammatory cytokines [14]. Along with the tumor itself, cancer treatment can also contribute to exacerbate the production of proinflammatory cytokines. Tissue destruction by surgery, chemotherapy or radiotherapy leads to damage-associated molecular patterns (DAMPs) on damaged tissue, which bind to pattern recognition receptors (PRRs) on leukocytes triggering the expression of the transcription factor nuclear factor-κ-β (NFκβ) and the production of proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, interferon-α (INF-α), and tumour necrosis factor-α (TNF-α) [15]. Experimental studies have further demonstrated that proinflammatory cytokines may be mediators of cognitive changes associated with cancer treatment, and the fluctuations of circulating cytokines have been suggested to mediate 'sickness behavior' in patients with cancer [16]. Despite the presence of high levels of proinflammatory cytokines in patients with CRC [17,18], research into the involvement of these molecules in the pathophysiology of depression and anxiety in these subjects is still in its infancy. In this study, we investigated whether proinflammatory cytokine levels are related to depression and anxiety in CRC patients in different stages of the antitumor therapy. An integral understanding of the molecular mechanisms involved in these disorders will allow the design of therapeutic interventions that lead to an improved quality of life and overall survival of CRC patients.

2. Material and methods

2.1. Study design

A total of 60 patients of both genders aged over 18 years old was selected by convenience sampling at the Clinical Hospital of the Faculty of Medicine of Ribeirão Preto. The minimum sample size (n = 20) was estimated according to cytokine plasma levels found in a pilot trial conducted by our group (SD = 0.3897114320), and those reported in previous studies [19–23]. The Control group was composed of 20 healthy volunteers free of any psychiatric or immune system disease. Eligible participants for the others groups were those diagnosed with colorectal cancer. Pre-chemotherapy group: patients who underwent surgical resection and who did not start adjuvant therapy (n = 20); Under-chemotherapy group: patients undergoing chemotherapy for about 3 months (n = 20) and Post-chemotherapy group: patients who have completed adjuvant chemotherapy regimen about 6 months ago (n = 20). Patients in pre-under-post-chemotherapy groups presented in clinical stage III (local tumor in colon or rectum that is larger than 5 cm in diameter and/or has spread to regional lymph nodes) according to staging system of the American Joint Committee on Cancer/Union for International Cancer Control [24]. All patients received adjuvant chemotherapy with capecitabine (2000 mg/m^2/day for 14 days orally every 21 days) and oxaliplatin (130 mg/m^2 intravenous D1 every 21 days) [25] regimen, according to the therapeutic scheme adopted in the hospital. The exclusion criteria were as follow: (a) individuals with a history of autoimmune or chronic inflammatory disease, active infectious conditions, renal disease or diabetes mellitus; (b) individuals who were previously received or are receiving radiotherapy or chemotherapy; (c) use of immunosuppressive drugs; (d) patients diagnosed with schizoaffective disorder, bipolar disorder, or panic disorder, and (e) individuals with cognitive impairment that prevents them from understanding the study design and answer the questionnaire. Hospitalization records were monitored seeking for volunteers who met the criteria. The first twenty hospitalized patients who met the proposed criteria to each specific group were evaluated during all the study period. Socio-demographic data included age, gender, education and marital status.

2.2. Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Only patients who agreed and signed the informed consent form participated in the study. The study was approved by the Ethics Committee of Ribeirão Preto College of Nursing.

2.3. Measures

Depression and anxiety were measured using the Brazilian-Portuguese validated version [26] of the Hospital Anxiety and Depression Scale (HADS) [27]. It consists of 14 items and contains two subscales: anxiety and depression. Each item is rated on a four-point scale, giving maximum scores of 21 for both subscales. Scores of 11 up to 21 on each subscale are considered to be a significant case of psychological morbidity, while scores of 8–10 represent the "borderline" and 0–7 normal. For the combined anxiety and depression score (total HADS score), a cut-off score of 19 was used to identify patients with severe affective psychopathology [28]. Blood samples (8 mL) were collected from all study participants in the morning, at the same range of hours (more or less 1-h difference) with vacuum tubes (Vacutainer-Becton Dickinson, Franklin Lakes, USA) and were allowed to clot for 1 h ± 5 min at 37 °C. After centrifugation at 1000*g* for 10 min at 4 °C, the serum was stored at −80 °C until use.

2.4. Cytokine analysis

The concentrations of IL-1β, IL-6, IL-8, IL-10, IL-12, TGF-β, and TNF-α were measured by Cytometric Bead Array (CBA) kits according to the manufacturer's instructions (BD Biosciences, San Diego, USA). CBA was performed with a BD™ FACSCanto flow cytometer. Quantitative analysis was done using FCAP Array™ Software.

2.5. Statistics

Data were analyzed using GraphPad Prism6 software (La Jolla, CA). To analyze the hypothesis of equal means between the groups, Kruskal-Wallis one way ANOVA followed by Dunn's multiple comparison posthoc test were used. The results were expressed as mean ± standard deviation (SD). Pearson correlation was performed to verify the correlation between variables. The significance level used for the tests was 5%.

3. Results

3.1. Demographic characteristics

Demographic characteristics of the study participants are shown in Table 1. Twenty healthy volunteers of both genders comprised the control group (mean age of 47.8 years, SD = 9.0, 60% female). Most of them were married (80%) and had secondary education (65%). Pre-chemotherapy group was composed of patients who underwent surgical resection but did not start adjuvant therapy (mean age of 56.8 years, SD = 7.2, 55% female). Almost half of them were married and had primary education. Patients undergoing chemotherapy (at about 3 months after starting treatment) formed the Under-chemotherapy group (mean age of 56.4 years, SD = 8.6, 50% female). The majority was married and half of them had secondary education. The Post-chemotherapy group consisted of patients who finished adjuvant chemotherapy about 6 months ago (mean age of 59.9 years, SD = 8.7, 50%

Table 1
Demographic characteristics of study participants.

Characteristics	Healthy volunteers n (%)	Pre- chemotherapy n (%)	Under- chemotherapy n (%)	Post-chemotherapy n (%)	P value
Age (mean ± SD)	47.8 ± 9	56.8 ± 7.2	56.4 ± 8.6	59.9 ± 8.7	ns[a]
Gender					
Male	8 (40)	9 (45)	10 (50)	10 (50)	ns[b]
Female	12 (60)	11 (55)	10 (50)	10 (50)	
Marital Status					
Single	2 (10)	7 (35)	7 (35)	6 (30)	ns[b]
Married	16 (80)	9 (45)	12 (60)	10 (50)	
Divorced	1 (5)	–	–	–	
Widowed	1 (5)	4 (20)	1 (5)	4 (20)	
Education level					
Primary	6 (30)	9 (45)	10 (50)	8 (40)	ns[b]
Secondary	13 (65)	6 (30)	8 (40)	9 (45)	
College/university	1 (5)	5 (25)	2 (10)	3 (15)	

[a] Kruskal-Wallis' posthoc Dunn's test.
[b] Pearson's Chi-square test.

female). Half of them were married and had secondary education (45%). We found no significant differences regarding age, gender, marital status, or education level among the groups.

3.2. HADS score

Table 2 shows the scores of anxiety and depression obtained by the study participants. In the control group, all individuals (100%) showed no anxiety or depression, whereas CRC patients in different stages of the antitumor therapy presented clinically significant levels of anxiety, depression, and a combination of severe depression and anxiety, indicated by HADS total score > 19 (Pre-chemotherapy group: 60%, 30%, 60%, respectively; Under-chemotherapy group: 30%, 65%, 60%, respectively, and Post-chemotherapy group: 25%, 25%, 40%, respectively).

3.3. Serum levels of cytokines

Most of the proinflammatory cytokines evaluated presented a similar pattern of production in which the highest levels were observed in CRC patients who did not start chemotherapy (Pre-chemotherapy group). In this group, IL-1β, IL-6, IL-8, and TNF-α concentrations were from 3.4 to 4.7-fold higher than in control group. Except for TNF-α, whose production increased up to 2-fold during and after chemotherapy, the production of these cytokines reduced upon treatment (Under and Post-chemotherapy groups), achieving levels similar to those of the control group. On the other hand, the lowest serum levels of IL-10 were observed in Pre-chemotherapy group (3-fold lower than control) and this cytokine levels gradually increased during the following steps of treatment (Under and Post-chemotherapy groups). In addition, there were no significant differences between the groups with respect to IL-12 and TGF-β concentrations (Fig. 1).

3.4. Correlations between serum levels of cytokines and HADS score

The correlations between HADS score and serum levels of each cytokine are shown in Table 3. No correlation was found in the control group. In CRC patients in different stages of the antitumor therapy, analysis revealed positive correlations of anxiety, depression, and anxiety/depression with IL-1β (Pre-chemotherapy group: r = 0.32, r = 0.22, r = 0.24, respectively; Under-chemotherapy group: r = 0.60, r = 0.26, r = 0.28, respectively; Post-chemotherapy group: r = 0.38, r = 0.28, r = 0.40, respectively), IL-6 (Pre-chemotherapy group: r = 0.47, r = 0.28, r = 0.79, respectively; Under-chemotherapy group: r = 0.55, r = 0.51, r = 0.45, respectively; Post-chemotherapy group: r = 0.27, r = 0.19, r = 0.22, respectively), IL-8 (Pre-chemotherapy group: r = 0.21, r = 0.23, r = 0.27, respectively; Under-chemotherapy group: r = 0.20, r = 0.50, r = 0.50, respectively; Post-chemotherapy group: r = 0.48, r = 0.28, r = 0.46, respectively) and TNF-α (Pre-chemotherapy group: r = 0.36, r = 0.24, r = 0.25, respectively; Under-chemotherapy group: r = 0.30, r = 0.38, r = 0.49, respectively; Post-chemotherapy group: r = 0.15, r = 0.14, r = 0.22, respectively)

Table 2
Depression and anxiety scores of study participants.

	Healthy volunteers n (%)	Pre-chemotherapy n (%)	Under chemotherapy n (%)	Post-chemotherapy n (%)	P value
Anxiety					
0–7	17 (85)	4 (20)	5 (25)	6 (30)	< 0.001[a]
8–10	3 (15)	4 (20)	9 (45)	9 (45)	
11–21	0 (0)	12 (60)	6 (30)	5 (25)	
Mean ± SD	3.2 ± 2.7	11 ± 3.7	10 ± 3	9.2 ± 3.3	
Depression					
0–7	20 (100)	5 (25)	3 (15)	3 (15)	< 0.001[a]
8–10	0 (0)	9 (45)	4 (20)	12 (60)	
11–21	0 (0)	6 (30)	13 (65)	5 (25)	
Mean ± SD	2.5 ± 2.3	9.9 ± 3.7	12 ± 3.2	9.3 ± 2.9	
Depression and anxiety (total HADS score)					
≤19	20 (100)	8 (40)	8 (40)	12 (60)	< 0.001[a]
> 19	0 (0)	12 (60)	12 (60)	8 (40)	

[a] Pearson's Chi-square test.

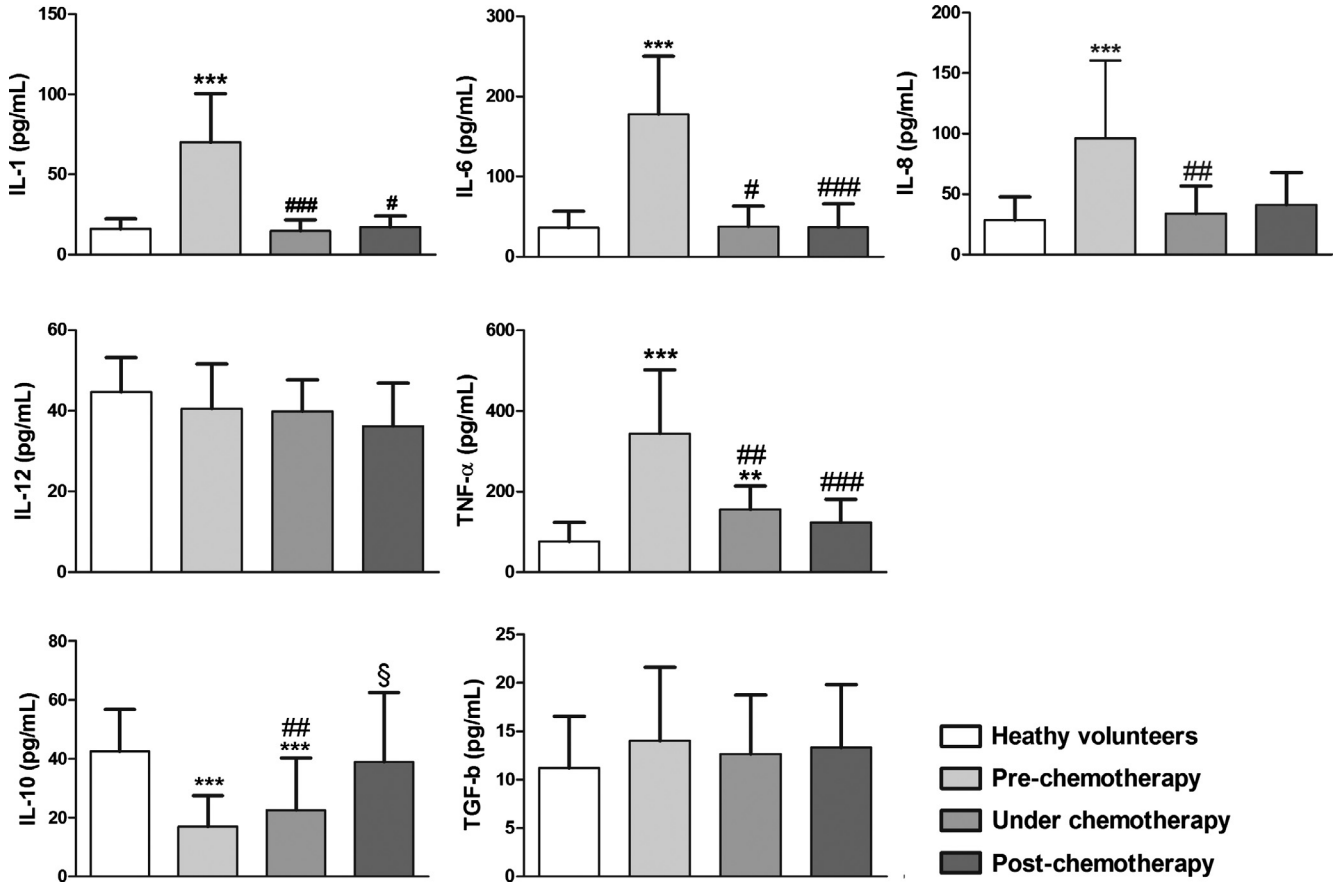

Fig. 1. Serum concentrations of the cytokines IL-1beta, IL-6, IL-8, TNF-alpha, IL-10, IL-12 and TGF-beta. Blood samples were collected from healthy volunteers, Post-operatory patients who did not start adjuvant chemotherapy treatment (Pre-chemotherapy group), Patients who were receiving chemotherapy treatment for at least three months (Under chemotherapy group), and Patients who concluded chemotherapy schemes at least 6 months ago (Post-chemotherapy group), and submitted to Cytometric Bead Array for cytokine quantification. Data were analyzed by Kruskal-Wallis test with Dunn post test and represent mean ± SD. *p < 0.05 *vs* Healthy volunteers, #P < 0.05 *vs* Pre-chemotherapy patients, §p < 0.05 *vs* Under Chemotherapy patients, n = 20 for each group.

and a negative correlation with IL-10 (Pre-chemotherapy group: r = –0.28, r = –0.25, r = –0.24, respectively; Post-chemotherapy group: r = –0.29, r = –0.12, r = –0.25, respectively). No associations were found between HADS score and IL-12 and TGF-β levels.

4. Discussion

In the current study, we investigated whether proinflammatory cytokine levels relate to depression and anxiety in CRC patients in

Table 3
Correlations between serum levels of cytokines and HADS score.

	IL-1	IL-6	IL-8	IL-10	IL-12	TNF-α	TGF-β
Healthy volunteers							
Anxiety (HADS)	0.19	0.12	0.18	−0.14	0.11	0.15	−0.11
Depression (HADS)	0.12	0.13	0.12	−0.17	0.17	0.08	−0.12
D and A (total HADS)	0.12	0.14	0.22	−0.16	0.14	0.09	−0.12
Pre-chemotherapy							
Anxiety (HADS)	0.32**	0.47***	0.21*	−0.28*	−0.20	0.36**	0.10
Depression (HADS)	0.22*	0.28*	0.23*	−0.25*	−0.10	0.24*	0.05
D and A (total HADS)	0.24*	0.79***	0.27*	−0.24*	−0.16	0.25*	0.05
Under-chemotherapy							
Anxiety (HADS)	0.60***	0.55***	0.20*	−0.15	−0.15	0.30*	−0.15
Depression (HADS)	0.26*	0.51**	0.50**	−0.14	−0.13	0.38**	−0.13
D and A (total HADS)	0.28*	0.45**	0.50**	−0.14	−0.12	0.49**	−0.09
Post-chemotherapy							
Anxiety (HADS)	0.38**	0.27*	0.48***	−0.29*	−0.12	0.15	−0.13
Depression (HADS)	0.28*	0.19	0.28*	−0.12	−0.21*	0.14	−0.14
D and A (total HADS)	0.40*	0.22**	0.46**	−0.25*	−0.13	0.22*	−0.19

HADS: Hospital Anxiety and Depression Scale; D and A: Depression and Anxiety combined (total HADS).
* p < 0.05 (Simple linear regression).
** p < 0.001 (Simple linear regression).
*** p < 0.0001 (Simple linear regression).

different stages of the antitumor therapy. We show that the levels of circulating cytokines fluctuated throughout the treatment. Patients evaluated before chemotherapy presented the highest concentrations of proinflammatory cytokines, whose levels decreased in the following steps of treatment. Lowest IL-10 serum levels were also verified in these patients, which were normalized until the end of the antitumor therapy. Clinically relevant scores of anxiety and/or depression were verified at every stage of treatment. IL-1β, IL-6, IL-8, and TNF-α correlated positively with depression and/or anxiety in CRC patients, while IL-10 correlated negatively.

There is a huge body of evidence to support that the immune system and the central nervous system communicate bidirectionally [11,29–31]. The "cytokine hypothesis" of depression/anxiety etiology suggests that behavioral changes observed in cancer patients are caused by proinflammatory cytokines produced by cells in the tumor microenvironment, which primarily affects the central nervous system function [32,33]. Binding to specific receptors on nerve cells, cytokines can influence the serotonin metabolism by altering the metabolism of tryptophan, which in turn affects the hypothalamic-pituitaryadrenal axis, leading to an increased inflammatory response to interrupt the functioning of glucocorticoid receptors [34]. Cytokines may also modify neural plasticity, as evidenced by structural findings and functional imaging changes in important neural networks associated with mood disorders such as hippocampus and other limbic and cortical regions [11]. Furthermore, high levels of the proinflammatory cytokines IL-1β and TNF-α have been demonstrated to upregulate the expression of the serotonin transporter in humans, increasing the reuptake of this monoamine and decreasing the serotonergic neurotransmission, which can lead to depressive behaviors [35,36]. These literature data, together with our results showing that CRC patients have elevated serum levels of IL-1β, IL-6, IL-8, and TNF-α, point to the existence of a biological origin for depression in these patients. This hypothesis is supported by studies showing a correlation between serum levels of proinflammatory cytokines and depressive symptoms in pancreatic and ovarian cancer patients [37,38]. The cytokine theory of depression is certainly attractive for a field that is short of real innovations.

In general, proinflammatory cytokines have been postulated to strongly influence the immunological status of cancer patients. In the present study, we found a similar pattern of proinflammatory cytokine production during the antitumor therapy. According to results previously reported [18,39–41], we observed that CRC patients who did not start adjuvant chemotherapy showed elevated levels of IL-1β, IL-6, IL-8, and TNF-α. These patients also presented the highest scores of depression and anxiety, possibly because in these stages of treatment they experience several stressors and emotional upheavals, such as the expectancy with the beginning of chemotherapy, fear of death, and interruption of life plans [42]. Compared to them, patients who were undergoing or have completed adjuvant chemotherapy had lower levels of proinflammatory cytokines, which may be related to chemotherapy-induced myelosuppression [43]. Otherwise, given that tumor cells themselves are an important source of cytokines [44], along other non-cancerous cell types [45] in tumor microenvironment, it is also plausible that their elimination by antiproliferative agents also contributes to reduced production of systemic cytokines. Even though proinflammatory cytokine levels reduced upon chemotherapy, they still correlated with depression and anxiety scores.

In consistency with such a reduction in circulating proinflammatory cytokine levels, patients who have finished the antitumor therapy also presented lower levels of anxiety and depression. Considering also the emotional dimensions of depression and anxiety, it is plausible to assume that it may be related in part to the fact that psychological symptoms tend to decrease over time, so that most patients with cancer have their standardized humor with the end of treatment [46]. Although our results showed that the levels of anxiety and depression decreased over antitumor treatment, a significant number of patients still had elevated levels of such disorders six months after chemotherapy has finished, an observation that points to the necessity that that all CRC patients, including those who finished treatment, are routinely screened for psychological distress.

Contrary to proinflammatory cytokines, we found lower serum levels of the anti-inflammatory cytokine IL-10 in CRC patients in the Pre-chemotherapy group, corroborating with previous studies that have reported decreased levels of IL-10 in CRC patients [17]. Except for CRC patients who were undergoing chemotherapy, we showed that IL-10 concentrations negatively correlated with anxiety/depression in patients who did not start or have completed adjuvant chemotherapy.

Limitations of this study include its cross-sectional nature, which prevented us to establish a cause-and-effect relationship, and the relative small number of colorectal patients studied. Another limitation of this study was the lack of control data from patients with only anxiety and depression, and from patients who had gone through surgery for other bowel diseases other than colorectal cancer; thus, a clear-cut correlation between cytokine dysregulation and depression/anxiety pathophysiology in CRC patients was not possible. Nevertheless, the finding that plasma concentrations of IL-1β, IL-6, IL-8, and TNF-α related with depression and/or anxiety in these subjects provided support for the continued examination of inflammation as a key influential factor in such psychological disorders. For future studies, it might be more appropriate to include also concurrent cancer controls without depression/anxiety as references so as the effects of the cancer itself on mood and cognitive changes can be taken into account. Our findings were only suggestive of a potential correlation between cytokines and depression/anxiety, and the identified correlations did not equate with causation.

Despite the limitations of this study, we believe it has important clinical and research implications. Taken into account that CRC patients with high levels of circulating proinflammatory cytokines may be at significant risk for developing depression and anxiety, cytokine levels may be a promissory marker for the manifestation of such psychological disorders in these patients. Moreover, the high incidence of depressive/anxiety symptoms among CRC patients, including those who finished treatment, emphasize the importance of effective diagnostic strategies for screening for emotional distress along the disease trajectory to detect patients that may be at high risk for poor adjustment to disease and its treatments. New therapeutic strategies to assist in alleviating mental suffering and pain in cancer patients might result from a better understanding of the role of cytokines in the pathophysiology of depression and anxiety in CRC patients.

In conclusion, our results show that CRC patients at different stages of the antitumor therapy presented high concentrations of circulating proinflammatory cytokines and that these levels oscillated throughout the treatment, potentially correlating with clinically significant levels of depression and/or anxiety, which suggest that cytokines are involved in the pathophysiology of these psychological disorders in CRC patients. In addition, the results indicate that depression and anxiety may not just be a reaction to a diagnosis of cancer but relate, at least in part, to immunological changes caused by the tumor itself.

Declaration of conflicting interests

All authors declare that there is no conflict of interest.

Funding

This work was supported by a grant for FAPESP (2011/17118-9 and 2013/01262-9).

Authorship

The authors would like to thank the staff of the Service of Clinical Oncology of Clinics Hospital at Ribeirão Preto School of Medicine for

help with participant recruitment and all the participants who generously gave their time to take part.

References

[1] J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, et al., Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012, Int. J. Cancer 136 (5) (2015) 359–386, http://dx.doi.org/10.1002/ijc.29210.

[2] Ministry of Health of Brazil, and National Cancer Institute, Estimates/2016 - Incidence of cancer in Brazil. INCA, Rio de Janeiro, Brazil, 2016. Available from: < http://www.inca.gov.br > [access date: 24-11-2016].

[3] J. Dunn, B. Lynch, M. Rinaldis, K. Pakenham, L. McPherson, N. Owen, et al., Dimensions of quality of life and psychosocial variables most salient to colorectal cancer patients, Psychooncology 15 (2006) 20–30, http://dx.doi.org/10.1002/pon.919.

[4] A. Schrepf, S.K. Lutgendorf, L.M. Pyter, Pre-treatment effects of peripheral tumors on brain and behavior: neuroinflammatory mechanisms in humans and rodents, Brain Behav. Immun. (2015) S0889–S1591, http://dx.doi.org/10.1016/j.bbi.2015.04.010.

[5] A.M. Krebber, L.M. Buffart, G. Kleijn, I.C. Riepma, R. de Bree, C.R. Leemans, et al., Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments, Psycho-Oncology 23 (2) (2014) 121–130, http://dx.doi.org/10.1002/pon.3409.

[6] T. Levin, Y. Alici, Anxiety disorders, in: J. Holland, W. Breitbart, P. Jacobsen (Eds.), Psycho-Oncology, 2nd ed., Oxford University Press, New York, NY, 2010, pp. 324–331.

[7] S.M.B. Bottino, F. Fráguas, W.F. Gattaz, Depression and cancer, Rev. Psiquiatr Clin. 36 (3) (2009) 109–115.

[8] N. Hulbert-Williams, R. Neal, V. Morrison, K. Hood, C. Wilkinson, Anxiety, depression and quality of life after cancer diagnosis: what psychosocial variables best predict how patients adjust? Psycho-Oncology 21 (8) (2012) 857–867.

[9] A. Alacacioglu, O. Binicier, O. Gungor, I. Oztop, M. Dirioz, U. Yilmaz, Quality of life, anxiety, and depression in Turkish colorectal cancer patients, Supportive Care in Cancer 18 (4) (2010) 417–421, http://dx.doi.org/10.1007/s00520-009-0679-2.

[10] E.M. Reiche, S.O. Nunes, H.K. Morimoto, Stress, depression, the immune system, and cancer, Lancet Oncol. 5 (10) (2004) 617–625.

[11] A.H. Miller, V. Maletic, C.L. Raison, Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression, Biol. Psychiatry 65 (9) (2009) 732–741, http://dx.doi.org/10.1016/j.biopsych.2008.11.029.

[12] T.L. Huang, C.C. Lin, Advances in biomarkers of major depressive disorder, Adv. Clin. Chem. 68 (2015) 177–204, http://dx.doi.org/10.1016/bs.acc.2014.11.003.

[13] S.I. Grivennikov, Immunity, inflammation, and cancer, Cell 140 (6) (2010) 883–899, http://dx.doi.org/10.1016/j.cell.2010.01.025.

[14] M. Quante, J. Varga, T.C. Wang, F.R. Greten, The gastrointestinal tumor microenvironment, Gastroenterology 145 (2013) 63–78, http://dx.doi.org/10.1053/j.gastro.2013.03.052.

[15] H.R. Smith, Depression in cancer patients: pathogenesis, implications and treatment (Review), Oncol. Lett. 9 (2015) 1509–1514, http://dx.doi.org/10.3892/ol.2015.2944.

[16] Y.T. Cheung, T. Ng, M. Shwe, H.K. Ho, K.M. Foo, M.T. Cham, et al., Association of proinflammatory cytokines and chemotherapy-associated cognitive impairment in breast cancer patients: a multi-centered, prospective, cohort study, Ann. Oncol. 26 (2015) 1446–1451, http://dx.doi.org/10.1093/annonc/mdv206.

[17] A. Szkaradkiewicz, R. Marciniak, I. Chudzicka-Strugala, A. Wasilewska, M. Drews, P. Majewski, et al., Proinflammatory cytokines and IL-10 in inflammatory bowel disease and colorectal cancer patients, Arch. Immunol. Ther. Exp. 57 (2009) 291–294, http://dx.doi.org/10.1007/s00005-009-0031-z.

[18] S.I. Grivennikov, M. Karin, Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage, Ann. Rheum. Dis. 70 (2011) i104–i108, http://dx.doi.org/10.1136/ard.2010.140145.

[19] J.E. Bower, P.A. Ganz, N. Aziz, J.L. Fahey, Fatigue and proinflammatory cytokine activity in breast cancer survivors, Psychosom. Med. 64 (2002) 604–611.

[20] T.F. Cormanique, L.E.D.F. de Almeida, C.A. Rech, D. Rech, C. Panis, Chronic psychological stress and its impact on the development of aggressive breast cancer, Einstein (Sao Paulo) 13 (2015) 352–356, http://dx.doi.org/10.1590/S1679-45082015AO3344.

[21] D. Oliveira Miranda, T.A. Soares de Lima, L. Ribeiro Azevedo, O. Feres, J.J. Ribeiro da Rocha, G. Pereira-da-Silva, Proinflammatory cytokines correlate with depression and anxiety in colorectal cancer patients, Biomed. Res. Int. 2014 (2014) 739650, http://dx.doi.org/10.1155/2014/739650.

[22] S.C. Sepah, J.E. Bower, Positive affect and inflammation during radiation treatment for breast and prostate cancer, Brain Behav. Immun. 23 (2009) 1068–1072, http://dx.doi.org/10.1016/j.bbi.2009.06.149.

[23] L.M. Thornton, B.L. Andersen, T.A. Schuler, W.E. Carson, A Psychological intervention reduces inflammatory markers by alleviating depressive symptoms: secondary analysis of a randomized controlled trial, Psychosom. Med. 71 (2009) 715–724, http://dx.doi.org/10.1097/PSY.0b013e3181b0545c.

[24] AJCC (American Joint Committee on Cancer) Cancer Staging Manual, in: Edge, SB, Byrd, DR, Compton, CC, et al. editors, 7th ed., Springer, New York, 2010, p.143.

[25] H.J. Schmoll, C. Twelves, W. Sun, M.J. O'Connell, T. Cartwright, E. McKenna, M. Saif, S. Lee, G. Yothers, D. Haller, Effect of adjuvant capecitabine or fluorouracil, with or without oxaliplatin, on survival outcomes in stage III colon cancer and the effect of oxaliplatin on post-relapse survival: a pooled analysis of individual patient data from four randomised controll, Lancet Oncol. 15 (2014) 1481–1492.

[26] N.J. Botega, M.R. Bio, M.A. Zomignani, C. Jr, W.A. Pereira Garcia, Mood disorders among inpatients in ambulatory and validation of the anxiety and depression scale HAD, J. Public Health 29 (5) (1995) 355–363.

[27] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (1983) 361–370.

[28] D. Razavi, N. Delvaux, C. Farvacques, E. Robaye, Screening for adjustment disorders and major depressive disorders in cancer patients, Br. J. Psychiatry 156 (1990) 79–83.

[29] B.S. Rabin, S. Cohen, R. Ganguli, D.T. Lysle, J.E. Cunnick, Bidirectional interaction between the central nervous system and the immune system, Crit. Rev. Immunol. 9 (1989) 279–312.

[30] L. Steinman, Connections between the immune system and the nervous system, Proc. Natl. Acad. Sci USA 90 (1993) 7912–7914.

[31] R. Dantzer, Cytokine-induced sickness behaviour: a neuroimmune response to activation of innate immunity, Eur. J. Pharmacol. 500 (1–3) (2004) 399–411.

[32] T. Rich, P.F. Innominato, J. Boerner, M.C. Mormont, S. Iacobelli, B. Baron, et al., Elevated serum cytokines correlated with altered behavior, serum cortisol rhythm, and dampened 24-hour rest-activity patterns in patients with metastatic colorectal cancer, Clin. Cancer Res. 11 (5) (2005) 1757–1764.

[33] R. Dantzer, J.C. O'Connor, G.G. Freund, R.W. Johnson, K.W. Kelley, From inflammation to sickness and depression: when the immune system subjugates the brain, Nat. Rev. Neurosci. 9 (1) (2008) 46–56.

[34] D.G.A. Janssen, R.N. Caniato, J.C. Verster, B.T. Baune, A psychoneuroimmunological review on cytokines involved in antidepressant treatment response, Hum. Psychopharmacol. Clin. Exp. 25 (3) (2010) 201–215, http://dx.doi.org/10.1002/hup.1103.

[35] M.E. Hernandez, D. Mendieta, M. Pérez-Tapia, et al., Effect of selective serotonin reuptake inhibitors and immunomodulator on cytokines levels: an alternative therapy for patients with major depressive disorder, Clin. Dev. Immunol. 2013 (2013), http://dx.doi.org/10.1155/2013/267871.

[36] A.R. Howerton, A.V. Roland, T.L. Bale, Dorsal raphe neuroinflammation promotes dramatic behavioral stress dysregulation, J. Neurosci. 34 (21) (2014) 7113–7123, http://dx.doi.org/10.1523/JNEUROSCI.0118-14.2014.

[37] E. Spath-Schwalbe, K. Hansen, F. Schmidt, H. Schrezenmeier, L. Marshall, K. Burger, et al., Acute effects of recombinant human interleukin-6 on endocrine and central nervous sleep functions in healthy men, J. Clin. Endocrinol. Metab. 83 (1998) 1573–1579.

[38] D.L. Musselman, A.H. Miller, M.R. Porter, A. Manatunga, F. Gao, S. Penna, et al., Higher than normal plasma interleukin-6 concentrations in cancer patients with depression: preliminary findings, Am. J. Psychiatry 158 (8) (2001) 1252–1257.

[39] J. Kamińska, M.M. Kowalska, M.P. Nowacki, M.G. Chwaliński, A. Rysińska, M. Fuksiewicz, CRP, TNF-alpha, IL-1ra, IL-6, IL-8 and IL-10 in blood serum of colorectal cancer patients, Pathol. Oncol. Res. 6 (1) (2000) 38–41.

[40] Y. Ning, H.J. Lenz, Targeting IL-8 in colorectal cancer, Expert Opin. Ther. Targets 16 (5) (2012) 491–497, http://dx.doi.org/10.1517/14728222.2012.677440.

[41] M. Krzystek-Korpacka, D. Diakowska, B. Kapturkiewicz, M. Bebenek, A. Gamian, Profiles of circulating inflammatory cytokines in colorectal cancer (CRC), high cancer risk conditions, and health are distinct: possible implications for CRC screening and surveillance, Cancer Lett. 337 (1) (2013) 107–114, http://dx.doi.org/10.1016/j.canlet.2013.05.033.

[42] P. Klemm, M. Miller, J. Fernsler, Demands of illness in people treated for colorectal cancer, Oncol. Nurs. Forum 27 (4) (2000) 633–639.

[43] J. Pander, J.A. Wessels, H. Gelderblom, T. van der Straaten, C.J. Punt, H.J. Guchelaar, Pharmacogenetic interaction analysis for the efficacy of systemic treatment in metastatic colorectal cancer, Ann. Oncol. 22 (5) (2011) 1147–1153, http://dx.doi.org/10.1093/annonc/mdq572.

[44] R. Kim, M. Emi, K. Tanabe, K. Arihiro, Tumor-driven evolution of immunosuppressive networks during malignant progression, Cancer 66 (11) (2006) 5527–5536, http://dx.doi.org/10.1158/0008-5472.CAN-05-4128.

[45] H. Li, X. Fan, J.M. Houghton, Tumor microenvironment: the role of the tumor stroma in cancer, J. Cell. Biochem. 101 (2007) 805–815, http://dx.doi.org/10.1002/jcb.21159.

[46] B.L. Andersen, B. Andersen, C. deProsse, Controlled prospective longitudinal study of women with breast cancer, J. Consult. Clin. Psychol. 57 (6) (1989) 692–697.