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Current Perspective

The pathogenesis of cancer related fatigue: Could increased activity of pro-inflammatory cytokines be the common denominator?

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ABSTRACT

Cancer related fatigue (CRF), defined as a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with daily functioning, is highly prevalent and probably the most underestimated and insufficiently treated complication in cancer patients. Therefore, unravelling the pathogenesis of CRF is of great importance allowing the identification of novel therapeutic targets. It is generally believed that the pathogenesis is multicausal, explaining why most therapeutic interventions directed towards only one potential causative factor are unsuccessful. In this regard, it is of interest that increased activity of pro-inflammatory cytokines might be a common denominator causing CRF. Detailed insight in the central role of increased activity of pro-inflammatory cytokines in CRF will hopefully offer an effective approach in the treatment of CRF by affecting a broad array of proposed causative factors such as anaemia, disturbances of the hypothalamic–pituitary–adrenal axis and altered brain serotonin metabolism.

1. Introduction

Due to rising cancer incidence and improved outcomes for patients, the prevalence of patients living with cancer has considerably increased and will continue to do so in the near future. As a result, more attention should be paid to symptoms impairing the quality of life of cancer patients. Of these, one of the most disturbing ones is fatigue. Cancer related fatigue (CRF) is defined by the National Comprehensive Cancer Network as a persistent subjective sense of tiredness related to cancer or cancer treatment that interferes with daily functioning. In contrast to the tiredness of healthy individuals, CRF has greater impact on daily life, is not proportional to activity and not (totally) relieved by rest, which results in a persistent sense of exhaustion. An additional feature is that fatigue in healthy persons can serve as a protective or satisfactory symptom, whereas for cancer patients it is often a distressing symptom with a huge impact on the quality of life.[1]

CRF has several dimensions, i.e. physical, mental and emotional. Numerous sophisticated multidimensional measures are presently available to determine the prevalence, type and severity of CRF in predefined populations.[2] With these assessment tools, the prevalence of CRF amongst untreated cancer patients has been reported as high as 75%,

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whereas in cancer patients treated with chemotherapy or radiotherapy the prevalence is even higher.[3] In clinical practice, however, these assessment tools are rarely used. Therefore, fatigue is probably the most underestimated and insufficiently treated complication in cancer patients, although it has been reported to be more distressing for cancer patients than nausea, vomiting or pain.[4]

Clinical trials investigating putative therapies for CRF are relatively scarce.[5] The pathogenesis of CRF is largely unknown but it is generally accepted that different physiological and psychosocial factors play a part.[6] In this review, the focus will be on the physiological factors contributing to fatigue amongst cancer patients. Unravelling the different causes underlying CRF is of great importance as this may allow identification of novel targets for treatment. However, it should be realised that treating only one potential cause might be unsuccessful, given the multicausal pathogenesis of CRF. In this respect, it is of interest that it can be hypothesised that increased activity of pro-inflammatory cytokines may be a common denominator in CRF. This review describes the possible pathophysiological mechanisms of CRF, i.e. anaemia, disturbances of the hypothalamic–pituitary–adrenal (HPA) axis and altered brain serotonin (5-HT) metabolism, with particular interest for the role of increased pro-inflammatory cytokine activity as possible common denominator. The focus will be on the pathogenesis of the *physical* dimension. An extensive description of assessment tools as well as the results of non-pharmacological interventions is beyond the scope of this review and has recently been described in elegant reviews elsewhere.[2,7]

2. Increased activity of pro-inflammatory cytokines

2.1. Pro-inflammatory cytokines and tumours

There is mounting evidence that ongoing inflammation plays a crucial role in tumour carcinogenesis as well as in tumour progression.[8] Tumour cells and adjacent normal tissue produce several cytokines and chemokines that attract various leukocytes including macrophages, dendritic cells and lymphocytes, which yield a tumour-induced inflammatory environment. The balance between pro- and anti-inflammatory cytokines determines the final effect on tumour development. An excess of pro-inflammatory cytokines has been found to promote the growth and survival of cancer cells, to promote angiogenesis, to stimulate DNA damage and to remodel the extracellular matrix so that invasion and migration of cancer cells are facilitated.[8] Once the tumour grows, tumour hypoxia arises inducing the production of pro-inflammatory cytokines by both tumour cells and normal cells in the inflammatory environment thereby creating a vicious circle.[8]

2.2. Pro-inflammatory cytokines and fatigue

Pro-inflammatory cytokines can induce fever, anorexia, cachexia, muscle cramps and also severe fatigue. A recently performed review of 20 clinical studies investigating the association between CRF and inflammatory markers amongst cancer patients showed a significant correlation between CRF and plasma levels of IL-6.[9]

In addition, given the hypothesis that administration of pro-inflammatory cytokines might have an anti-tumour activity, phase I studies with recombinant TNF-α, IL-6 and IFN-α in cancer patients have been performed, with fever, anorexia, myalgia and fatigue being the most common side effects.[10–12] Additional evidence for a causal role of pro-inflammatory cytokines in fatigue came from a small study amongst patients with Castleman disease. Castleman disease is a lymphoproliferative disorder characterised by systemic lymphadenopathy, constitutional inflammatory symptoms and dysregulated over production of IL-6. Treatment of these patients with humanised monoclonal antibodies against IL-6 (with an increasing dose to a maximum of 100 mg, twice a week, intravenously) showed an impressive relief from fatigue, immediately after the first administration. Furthermore, the increased C-reactive protein (CRP) levels, being a surrogate marker of IL-6 activity, normalised within two weeks after starting the anti-IL-6 therapy. Besides a transient decrease in granulocyte count in two patients with a spontaneous recovery, there were no side effects.[13]

2.3. Pro-inflammatory cytokines, anti-cancer therapy and CRF

Also the high incidence of CRF in patients who underwent chemo- or radiotherapy might be due to the increase of pro-inflammatory activity. Administration of etoposide in mice clearly induces IL-6 production correlating with a decrease in voluntary wheel running ($r = -0.57$; $p = 0.001$).[14] In a small study, radiotherapy of male patients with prostate cancer showed a correlation between elevated levels of IL-1 and CRF. Furthermore, paclitaxel administration amongst cancer patients showed increased levels of IL-6, IL-8 and IL-10. Increased levels of IL-10 were associated with joint pain and the increased levels of IL-8 with flu-like symptoms.[15] Finally, Monk et al. have hypothesised that docetaxel-induced fatigue (which is the dose limiting toxicity in a weekly schedule) could be diminished by adding a monoclonal antibody directed towards TNF-α to docetaxel. Amongst cancer patients ($n = 18$) assigned to weekly docetaxel plus anti-TNF-α therapy, a higher intended dose of docetaxel could be delivered (35 of the 36 doses) as compared to those patients ($n = 6$) assigned to docetaxel monotherapy (29 of the 36 doses). Moreover, escalating the dose of docetaxel (from 43 mg/m^2 to 52 mg/m^2) combined with anti-TNF-α therapy resulted in neutropeania but not fatigue, as limiting the adverse effect.[16] These data suggest that an increase in pro-inflammatory cytokine activity induced by cytoreductive therapy might cause CRF.

2.4. Pro-inflammatory cytokines and its association with anaemia, dysregulation of HPA-axis and altered serotonin metabolism

Enhanced pro-inflammatory cytokine activity has been associated with the development of several potential pathogenic biological processes in CRF, such as cancer related anaemia, dysregulation of the HPA-axis and altered serotonin metabolism. Therefore, enhanced pro-inflammatory cytokine activity

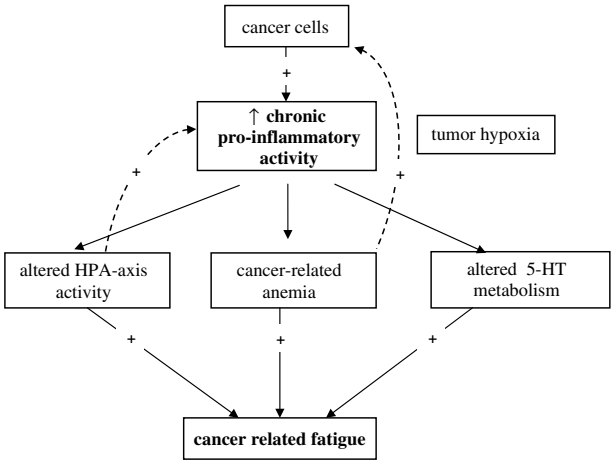

Fig. 1 – Proposed pathophysiological mechanisms in the development of cancer related fatigue.

could be the common denominator in CRF (Fig. 1). These three potential pathogenic processes in CRF will be described below with particular focus on its association with pro-inflammatory cytokines.

3. Anaemia

3.1. *Anaemia in cancer patients*

Recently, the European Cancer Anaemia Survey (ECAS), a large prospective survey that enrolled more than 15,000 treated and untreated patients with various types of cancers, established the prevalence of anaemia (haemoglobin <12 g/dl, i.e. <7.4 mmol/l) to be 39%. Amongst cancer patients not anaemic at the start of anti-tumour therapy, the incidence of anaemia after chemotherapy was 63%, after chemo-radiotherapy 40% and after radiotherapy alone 20%. The prevalence seems to be independent of the tumour type, but increases with age.[17] Fatigue is considered to be the cardinal symptom of anaemia.[18] Accordingly, low haemoglobin levels are associated with poorer overall quality of life as compared to higher levels.[19,20] In addition to deteriorating the quality of life, a growing body of evidence indicates that anaemia amongst cancer patients might also affect treatment response negatively and could be associated with impaired survival (Fig. 2).[21,22]

3.2. *Aetiology of anaemia in cancer patients*

Besides the well-known causes of anaemia, such as bone marrow suppression by cytoreductive therapy or tumour infiltration, nutritional deficiency, haemolysis or renal impairment, a separate *cancer-related anaemia* can be distinguished. It is thought that interaction of cancer cells with the immune system leads to the release of several pro-inflammatory cytokines such as TNF-α, IL-1α, IL-1β, INF-β and INF-γ. These cytokines induce the production of hepcidin in liver cells. Hepcidin diminishes, via internalisation of ferroportin, the liberation of iron from duodenal cells and reticulo-endothelial cells and thereby leads to a decrease in iron availability. In addition, these cytokines induce apoptosis of erythroid precursor cells and decrease the erythropoietin production, thereby diminishing erythropoiesis (Fig. 2).[18]

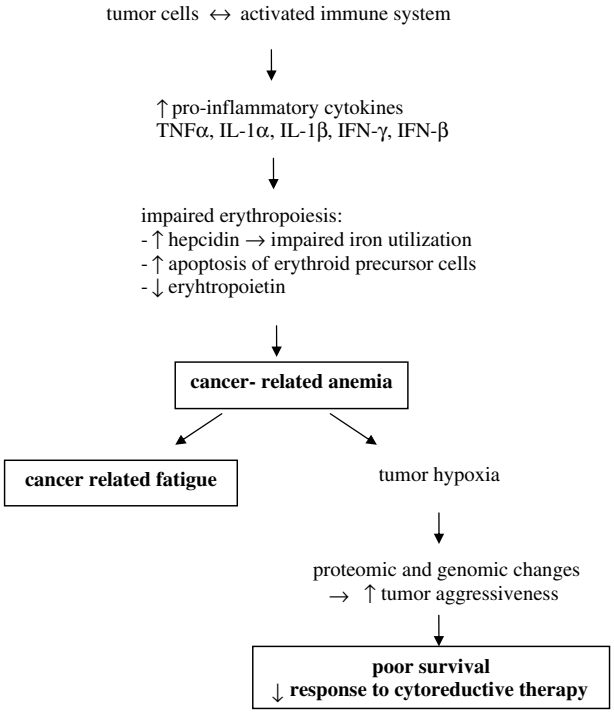

Fig. 2 – Proposed mechanism in the pathogenesis of cancer-related anaemia and its link to poor response to cytoreductive therapy and impaired survival.

3.3. *Clinical trials on anaemia in cancer patients*

To improve symptoms of fatigue related to anaemia, transfusion of red blood cells was the only available treatment until recombinant human epoetins (erythropoietin or darbepoetin) was introduced. In a systematic review including a total of 57 randomised studies with 9353 cancer patients, the majority treated with chemotherapy, there was consistent evidence that administration of epoetins to cancer patients with anaemia (haemoglobin [Hb] <12 g/dl, i.e. <7.4 mmol/l) increases the haemoglobin level, independent of red blood cell transfusion.[23] The relative risk (RR) for hematological response defined as an increase in haemoglobin level of 2 g/dl or more was 3.4 (3.1–3.8) for those treated with epoetins as compared to placebo. Furthermore, epoetins reduced the RR to receive red blood cell transfusion as compared to placebo (RR 0.67 [0.62–0.7]). Moreover, quality of life improved following epoetin administration. The extent of improvement however, was difficult to establish because of the different measurements used to quantify, the quality of life.[23] In an analysis of data from six trials, which used the FACT-fatigue subscale, a clinically significant but just small effect was found.[24]

3.4. *Conclusions*

Anaemia, with fatigue as the cardinal symptom, is common amongst cancer patients and might be caused by an increased

activity of pro-inflammatory cytokines. Although symptomatic treatment with blood transfusion or epoetins seems to improve the quality of life, complications have been reported. Consequently, it would be of interest to explore the pathogenic role of pro-inflammatory cytokine activity in (cancer-related) anaemia to explore the possibility of anti-inflammatory treatment of cancer-related anaemia.

4. Disturbances in hypothalamic–pituitary–adrenal (HPA) axis

4.1. *Function of the HPA axis*

Under physiological conditions, cortisol is released from the adrenals in a circadian rhythm. The biological function of cortisol is diverse, ranging from regulation of protein, carbohydrate and fat metabolism and the extracellular fluid volume to its anti-inflammatory properties. The symptoms of hypocortisolism, such as fatigue, anorexia, weight loss, arthralgia, myalgia, sleep disturbance and mood disorders, resemble the symptoms of CRF. As a result, dysregulation of the HPA-axis is proposed to play a role in CRF.

4.2. *Dysregulation of HPA-axis is hypothesised to play a role in CRF*

The effect of distressing events on the HPA axis depends on the duration of exposure. An acute release of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF-α, leads to stimulation of the HPA axis and thereby to increased cortisol levels.[25] However, long term exposure to pro-inflammatory stimuli was found to dishabituate the stimulation of the HPA axis resulting in a decreased cortisol syntheses and/or a blunted circadian secretory rhythm.[26] Therefore, it has been hypothesised that cancer-associated chronic elevated pro-inflammatory cytokines lead to dysregulation of HPA-axis thereby causing CRF.

4.3. *Clinical support for a role of dysregulation of the HPA axis in CRF*

Studies exploring the association between absolute decreased levels of cortisol or blunted cortisol response to stimuli and CRF are scarce. Amongst breast cancer survivors CRF was indeed associated with lower levels of cortisol as compared to those without CRF,[27] however, this could not be confirmed amongst patients with active cancer.[28] Amongst breast cancer survivors with persistent fatigue, the artificial stress stimulus LPS yielded a significantly less salivary cortisol increase and a significantly greater increase of the pro-inflammatory cytokines IL-1β and IL-6 compared to non-fatigue participants.[27] Whether this altered response of the HPA axis in terms of glucocorticoid release and glucocorticoid sensitivity is indeed involved in CRF is still a matter of debate.

Two clinical trials have investigated the effect of glucocorticoid administration on CRF.[29,30] In both trials a favourable effect on fatigue (68% increase in daily activity[30] or a significant improvement in 2 of the 3 factors measured by the Piper fatigue scale[29]) was observed. The sample sizes of the studies, however, were small (40 and 84 patients), whilst different formulas of glucocorticoids were used (methylprednisolon 16 mg bid or megastrol acetate 160 mg tid), and the duration of treatment was short (10–14 days). Although the short-term administration of glucocorticoids might be effective in diminishing CRF, its long-term use might be limited to only cancer patients in terminal phase, given the well-known adverse-effects.

4.4. *Conclusion*

Chronic cancer-related elevated pro-inflammatory cytokines might lead to dysregulation of HPA-axis thereby causing CRF. Sporadic clinical data support this hypothesis as immuno-suppressive therapy with glucocorticoids was found to improve the activity and diminish fatigue. Further research to establish a causal role of increased pro-inflammatory cytokine activity in the pathogenesis of a disturbed HPA axis in CRF, however, is a prerequisite before new therapeutic options can be explored.

5. Altered brain serotonin metabolism

5.1. *Serotonin (5-HT) metabolism and its link to CRF*

Serotonin (5-hydroxytryptamine; 5-HT) is a mono-amine neurotransmitter produced in the synapses by decarboxylation of the amino acid tryptophan. Serotonin has diverse and often reverse actions, depending on to which receptor and which exact location it binds. There are seven 5-HT receptor families with at least 21 subtypes, most of them located in the central nervous system.

Serotonin is involved in many biological processes, such as the regulation of appetite, mood, sleep, memory, learning and muscle contraction. Since these biological processes are also dysregulated in CRF, it has been hypothesised that altered levels of synaptic 5-HT might play an important role in the pathogenesis of CRF. The main problem in the investigation of this hypothesis is the lack of possibilities to accurately measure the neurotransmitter synaptic activity in the brain. Therefore, direct evidence for this hypothesis is scarce, mainly based on animal studies and non-cancer patients and often showing seemingly conflicting results. For example, some investigators suggest an association between increased levels of 5-HT and fatigue, whilst others suggest the opposite.

5.2. *Elevated synaptic levels of 5-HT and its association with CRF*

Injecting L-tryptophan, an amino acid precursor of 5-HT, in a cerebral ventricle of male Wistar rats showed a significant reduction in running time to exhaustion (17.7 ± 13 min versus 35.8 ± 4.9 min) and work load (6.7 ± 0.6 kg m versus 14.3 ± 1.9 kg m) as compared to placebo.[31] Similarly, intraperitoneal administration of a 5-HT agonist in rats did induce impaired running time to exhaustion which was reversible with a 5-HT antagonist.[32] Also in men, prolonged physical activity-induced exhaustion is thought to be caused by increased levels of brain tryptophan which subsequently stimulate 5-HT synthesis and release.[33] This is supported by the fact that elevated synaptic 5-HT levels, induced by administration of a

selective serotonin re-uptake inhibitor (SSRI), did reduce the physical capability of healthy volunteers.[34] Altogether, these data suggest an association between increased synaptic 5-HT levels and the severity of fatigue.

Also other studies point to a role of 5-HT in fatigue. Some supporting evidence for this hypothesis comes from studies amongst non-cancer patients treated with 5-HT_3 receptor antagonists, ondansetron and granisetron. These antagonists bind to the 5-HT_3 receptor present on enteric neurons causing its well-known anti-emetic effect. However, these receptors are also present on the neurons of the brain and spinal cord, contributing to central effects of 5-HT. The first evidence was described in a case report, in which a women with chronic hepatitis C infection and severe symptoms of fatigue was intermittently treated with ondansetron, showing a remarkable association with relief of fatigue.[35] Further evidence came from small studies amongst patients with chronic fatigue syndrome ($n = 5$; granisetron maximum of 2 mg a day), chronic hepatitis B infection ($n = 36$; ondansetron 4 mg bid) and primary biliary cirrhosis ($n = 60$; ondansetron 4 mg tid) showing a significant decrease in fatigue severity after 4 and 8 weeks of treatment with 5-HT_3 receptor antagonists, respectively.[36,37]

5.3. *Decreased synaptic levels of 5-HT and its association with CRF*

Besides *elevated* synaptic levels of 5-HT, it has been suggested that *decreased* levels of brain 5-HT might be the underlying pathological state causing CRF. There is a growing body of evidence from in vivo studies which suggests that elevated pro-inflammatory cytokines such as IL-2, INF-γ, or TNF-α activate the tryptophan- and 5-HT-degrading enzyme indoleamine 2,3-dioxygenase (IDO) causing decreased levels of synaptic 5-HT (Fig. 3).[38] Moreover, enhanced pro-inflammatory cytokines activity also stimulates the 5-HT transporters causing enhanced 5-HT re-uptake also resulting in decreased levels of synaptic 5-HT (Fig. 3).[39] Thus, increased pro-inflammatory cytokine activity might cause decreased levels of 5-HT. There is convincing evidence suggesting that light physical exercise is an effective therapy for diminishing CRF amongst cancer survivors.[40] The proposed mechanism through which physical activity might affect the severity of fatigue is by increasing the levels of free tryptophan in plasma and in the brain resulting in enhanced pre-synaptic 5-HT synthesis. On the other hand, as mentioned before, prolonged physical activity in men (presumably causing massive synaptic 5-HT increase) has shown to induce chronic symptoms of fatigue.[33] These findings could be explained by proposing the association between 5-HT levels and fatigue to be *U*-shaped (Fig. 4), i.e. light physical activity causes normalisation of the decreased 5-HT levels (relieve of fatigue) whereas prolonged physical activity leads to increased levels of 5-HT causing fatigue.

This explanation also holds true for the association between depression and fatigue. Amongst cancer patients depression often coexists with CRF. Symptoms of depression are caused by abnormalities of different neurotransmitters in various brain regions, including *decreased* synaptic levels of 5-HT.[41] Treatment with SSRI's could then affect both symptoms of depression and of fatigue. In a large study amongst 549 cancer patients developing fatigue after one course of chemotherapy who were randomly assigned to the SSRI paroxetine or placebo, depression was significantly reduced amongst those using paroxetine as compared to those using placebo, however fatigue was not.[42] These findings were confirmed in a smaller study ($n = 94$) amongst breast cancer patients receiving chemotherapy who were randomly assigned

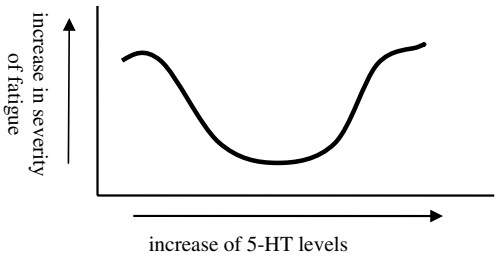

Fig. 4 – Possible association between serotonin (5-HT) levels and fatigue.

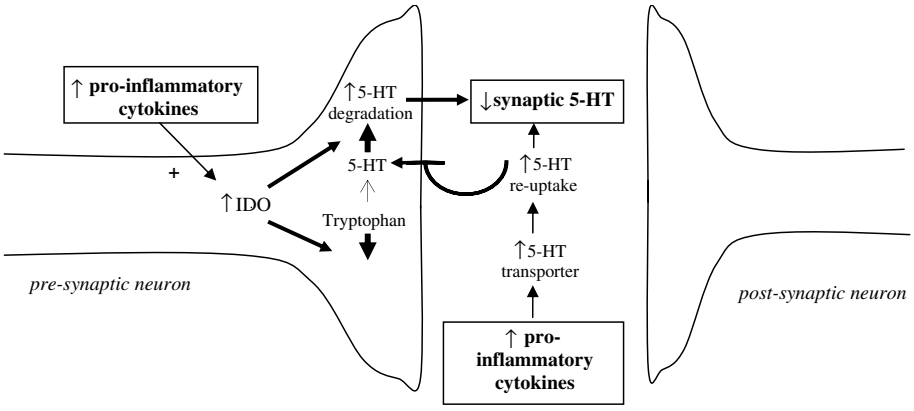

Fig. 3 – Proposed mechanism of enhanced pro-inflammatory cytokine activity leading to decreased synaptic 5-HT levels. Increased activity of pro-inflammatory cytokines leads to stimulation of the enzyme indoleamine 2,3-dioxygenase (IDO) causing enhanced tryptophan en serotonin (5-HT) degradation on the one hand and to increased activity of the 5-HT transporters on the other, both leading to decreased levels of synaptic 5-HT.

to paroxetine or placebo.[43] The SSRI's could cause a massive elevation in synaptic level of 5-HT higher than the optimal 5-HT level (Fig. 4), resulting in diminishing of the depression however not relieving fatigue.

5.4. *Conclusion*

It could be hypothesised that altered levels of synaptic 5-HT might play an important role in the pathogenesis of CRF in a *U*-shape manner, i.e. there is an optimal 5-HT level without symptoms of fatigue, whereas lower or higher 5-HT levels are associated with fatigue. Interestingly, increased activity of pro-inflammatory cytokines are known to decrease synaptic 5-HT levels by increasing the degradation of 5-HT and by enhancing 5-HT re-uptake, which support a role of pro-inflammatory cytokines in the 5-HT metabolism. Nevertheless, more research is necessary to substantiate this hypothesis.

6. Final conclusion

The pathogenesis of CRF is largely unknown, probably many different factors might play a role. In cross-sectional as well as longitudinal studies CRF has been correlated with anaemia, dysregulation of the HPA-axis, altered serotonin metabolism and elevated pro-inflammatory cytokine activity, suggesting that these factors might play an etiological role in CRF.[44] However, a correlation does not necessarily mean a cause. One of the main obstacles in determining causative factors in CRF is the inability to develop animal models. To circumvent this lack, clinical intervention trials have been performed in which the proposed causative factors were modulated. However, neither of the aforementioned factors is essential nor predominant to explain CRF in patients. Therefore, intervention trials in patients with CRF affecting only one potential cause probably oversimplify the pathogenesis of CRF. This might well be the explanation of the often disappointing results in clinical intervention trials. Therefore, future research on the pathogenesis of CRF should aim at defining underlying common denominators in CRF. A chronic pro-inflammatory state is proposed to be one such common denominator, inducing cancer-related-anaemia, dysregulation of the HPA-axis and altered serotonin metabolism, all being reported as putative causal factors in CRF (Fig. 1). It is of interest to collect further evidence for a role of increased pro-inflammatory cytokine activity as this would provide new tools for targeted therapy in CRF, such as monoclonal antibody therapy or targeting down-stream signal transduction pathways.

Conflict of interest statement

None declared.

REFERENCES

1. Stone P, Richardson A, Ream E, Smith AG, Kerr DJ, Kearney N. Cancer-related fatigue: inevitable, unimportant and untreatable? Results of a multi-centre patient survey. Cancer Fatigue Forum. *Ann Oncol* 2000;**11**:971–5.
2. Jean-Pierre P, Figueroa-Moseley CD, Kohli S, Fiscella K, Palesh GR, Morrow GR. Assessment of cancer-related fatigue: implications for clinical diagnosis and treatment. *Oncologist* 2007;**12**(Suppl. 1):11–21.
3. Hofman M, Ryan JL, Figueroa-Moseley CD, Jean-Pierre P, Morrow GR. Cancer-related fatigue: the scale of the problem. *Oncologist* 2007;**12**(Suppl. 1):4–10.
4. Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist* 2000;**5**:353–60.
5. Carroll JK, Kohli S, Mustian KM, Roscoe JA, Morrow GR. Pharmacologic treatment of cancer-related fatigue. *Oncologist* 2007;**12**(Suppl. 1):43–51.
6. Ahlberg K, Ekman Tor, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet* 2003;**362**:640–50.
7. Mustian KM, Morrow GR, Carroll JK, Figueroa-Moseley P, Jean-Pierre P, Williams GC. Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. *Oncologist* 2007;**12**(Suppl. 1):52–67.
8. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;**420**:860–7.
9. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun* 2007;**21**:413–27.
10. Malik UR, Makower DF, Wadler S. Interferon-mediated fatigue. *Cancer* 2001;**92**:1664–8.
11. Hieber U, Heim ME. Tumor necrosis factor for the treatment of malignancies. *Oncology* 1994;**51**(2):142–53.
12. Sosman JA, Aronson FR, Sznol M, et al. Concurrent phase I trials of intravenous interleukin 6 in solid tumor patients: reversible dose-limiting neurological toxicity. *Clin Cancer Res* 1997;**3**(1):39–46.
13. Nishimoto N, Kanakura Y, Aozasa K, et al. Humanized anti-interleukin-6 receptor antibody treatment of multicentric Castleman disease. *Blood* 2005;**106**:2627–32.
14. Wood LJ, Nail LM, Perrin NA, Elsea CR, Fischer A, Druker BJ. The cancer chemotherapy drug etoposide (VP-16) induces proinflammatory cytokine production and sickness behavior-like symptoms in a mouse model of cancer chemotherapy-related symptoms. *Biol Res Nurs* 2006;**8**:157–69.
15. Pusztai L, Mendoza TR, Reuben JM, et al. Changes in plasma levels of inflammatory cytokines in response to paclitaxel chemotherapy. *Cytokine* 2004;**25**:94–102.
16. Monk JP, Phillips G, Waite R, 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* 2006;**24**:1852–9.
17. Ludwig H, Van Belle S, Barrett-Lee P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer* 2004;**40**:2293–306.
18. Birgegard G, Aapro MS, Bokemeyer C, et al. Cancer-related anemia: pathogenesis, prevalence and treatment. *Oncology* 2005;**68**(Suppl. 1):3–11.
19. Fallowfield L, Gagnon D, Zagari M, et al. Multivariate regression analyses of data from a randomised, double-blind, placebo-controlled study confirm quality of life benefit of epoetin alfa in patients receiving non-platinum chemotherapy. *Br J Cancer* 2002;**87**(12):1341–53.
20. Echteld MA, Passchier J, Teunissen S, Claessen S, de Wit R, van der Rijt CC. Multidimensional fatigue and its correlates in

hospitalised advanced cancer patients. *Eur J Cancer* 2007;**43**(6):1030–6.
21. Blohmer JU, Dunst J, Harrison L, et al. Cancer-related anemia: biological findings, clinical implications and impact on quality of life. *Oncology* 2005;**68**(S1):12–21.
22. Vaupel P, Kelleher DK, Hockel M. Oxygen status of malignant tumors: pathogenesis of hypoxia and significance for tumor therapy. *Semin Oncol* 2001;**28**:29–35.
23. Bohlius J, Wilson J, Seidenfeld J, et al. Erythropoietin or darbepoetin for patients with cancer. *Cochrane Database Syst Rev* 2006;**3**:CD003407.
24. Rizzo JD, Somerfield MR, Hagerty KL, et al. American Society of Clinical Oncology/American Society of Hematology 2007 clinical practice guideline update on the use of epoetin and darbepoetin. *J Clin Oncol*, 2007; **25**: in press. [Epub ahead of print].
25. Wichers M, Maes M. The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. *Int J Neuropsychopharmacol* 2002;**5**:375–88.
26. Shanks N, Harbuz MS, Jessop DS, Perks P, Moore PM, Lightman SL. Inflammatory disease as chronic stress. *Ann NY Acad Sci* 1998;**840**:599–607.
27. Bower JE, Ganz PA, Aziz N. Altered cortisol response to psychologic stress in breast cancer survivors with persistent fatigue. *Psychosom Med* 2005;**67**:277–80.
28. Lundstrom S, Furst CJ. Symptoms in advanced cancer: relationship to endogenous cortisol levels. *Palliat Med* 2003;**17**:503–8.
29. Bruera E, Ernst S, Hagen N, et al. Effectiveness of megestrol acetate in patients with advanced cancer: a randomized, double-blind, crossover study. *Cancer Prev Control* 1998;**2**:74–8.
30. Bruera E, Roca E, Cedaro L, Carraro S, Chacon R. Action of oral methylprednisolone in terminal cancer patients: a prospective randomized double-blind study. *Cancer Treat Rep* 1985;**69**:751–4.
31. Soares DD, Coimbra CC, Marubayashi U. Tryptophan-induced central fatigue in exercising rats is related to serotonin content in preoptic area. *Neurosci Lett* 2007;**415**:274–8.
32. Bailey SP, Davis JM, Ahlborn EN. Serotonergic agonists and antagonists affect endurance performance in the rat. *Int J Sports Med* 1993;**14**:330–3.
33. Fernstrom JD, Fernstrom MH. Exercise, serum free tryptophan, and central fatigue. *J Nutr* 2006;**136**:553S–9S.
34. Wilson WM, Maughan RJ. Evidence for a possible role of 5-hydroxytryptamine in the genesis of fatigue in man: administration of paroxetine, a 5-HT re-uptake inhibitor, reduces the capacity to perform prolonged exercise. *Exp Physiol* 1992;**77**:921–4.
35. Jones EA. Relief from profound fatigue associated with chronic liver disease by long-term ondansetron therapy. *Lancet* 1999;**354**:397.
36. Piche T, Vanbiervliet G, Cherikh F, et al. Effect of ondansetron, a 5-HT3 receptor antagonist, on fatigue in chronic hepatitis C: a randomised, double blind, placebo controlled study. *Gut* 2005;**54**:1169–73.
37. Theal JJ, Toosi MN, Girlan L, et al. A randomized, controlled crossover trial of ondansetron in patients with primary biliary cirrhosis and fatigue. *Hepatology* 2005;**41**: 1305–12.
38. Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. *Mol Psychiatry* 2007;**12**:988–1000.
39. Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. *Neuropsychopharmacology* 2006;**31**:2121–31.
40. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:1588–95.
41. Milak MS, Parsey RV, Keilp J, Oquendo MA, Malone KM, Mann JJ. Neuroanatomic correlates of psychopathologic components of major depressive disorder. *Arch Gen Psychiatry* 2005;**62**:397–408.
42. Morrow GR, Hickok JT, Roscoe JA, et al. Differential effects of paroxetine on fatigue and depression: a randomized, double-blind trial from the University of Rochester Cancer Center Community Clinical Oncology Program. *J Clin Oncol* 2003;**21**:4635–41.
43. Roscoe JA, Morrow GR, Hickok JT, et al. Effect of paroxetine hydrochloride (Paxil) on fatigue and depression in breast cancer patients receiving chemotherapy. *Breast Cancer Res Treat* 2005;**89**:243–9.
44. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: a critical appraisal. *Eur J Cancer* 2006;**42**: 846–63.