Original paper

Maciej Bączyk[1], Lidia Gorzelińska[2], Marlena Pisarek[1], Paweł Gut[1], Jerzy Sowiński[1], Jacek Łuczak[2]
[1]Department of Endocrinology, University of Medical Sciences, Poznań, Poland
[2]Department of Palliative Medicine, University of Medical Sciences, Poznań, Poland

The potential influence of the applied treatment on selected endocrine and non endocrine parameters and general status of the patients with cancer cachexia syndrome

Abstract

The aim of the study was to establish correlation between the grade of cachexia and possible endocrine and non endocrine factors and the type of therapy (NSAID, corticosteroids, progestagens). 98 patients aged 36––70 years (mean— 55 years) with various degree of cancer cachexia were qualified to the study. Statistically significant, positive correlation between weight loss and: anorexia ($p < 0.01$), pain intensity ($p < 0.01$), grade of depression ($p < 0.01$), higher values of cortisol ($p < 0.05$) was detected. The progestagens are the most effective agents in the treatment of cancer cachexia, but good symptom control and psychological status of patient are also very important.

Key words: cancer cachexia, cortisol, cytokines, progestagens

Introduction

Cancer cachexia is mainly manifested by loss of weight and appetite with depletion of adipose and muscle tissue, easy satiation, general weakness, dysfunction of immune system and metabolic disorders. It is present in 75% of patients with advanced tumour. Clear diagnostic criteria of cancer cachexia have not been established up to now [1–3]. One of the main cachexia-inducing factors are blood pro-inflammatory cytokines, excreted by lymphocytes and monocytes/macrophages in response to the presence of the tumour, such as interleukines (IL), mainly IL-1 and IL-6, tumour necrosis factor α (TNFα), interferons (IFNs), mainly IFNα and IFNγ. The second group of cancer cachexia causes are tumour catabolic factors i.e. lipid mobilising factor (LMF) and protein mobilising factor (PMF) [4–7]. The third group of cancer cachexia causes are hormonal and metabolic disturbances. Dysfunction of carbohydrates metabolism results in an increase in aminoacid and lactate gluconeogenesis, activation of the Cori cycle, increase in glucose metabolism, changes in insuline concentration, insuline resistance with increased glucose intolerance. Main protein metabolism disturbances are as follows: increased muscle tissue metabolism, increased total protein metabolism with the growth of acute phase proteins syn-

Address for correspondence: Maciej Bączyk
University of Medical Sciences, Department of Endocrinology
ul. Przybyszewskiego 49, 60–355 Poznań, Poland
Tel: +48 61 869 13 30, fax: +48 61 869 16 82
e-mail: mpd@onet.eu

Advances in Palliative Medicine 2008, 7, 9–14

thesis and decrease in muscle proteins biosynthesis. Lipid metabolism changes include decrease in lipogenesis, increase in lipolysis, decrease in lipoprotein lipase activity, increase of glycerol and hyperlipidaemia levels [1–4, 9].

Anorexia *i.e.* appetite disturbances and decreased food intake is one of the most common symptoms in patients with cancer cachexia. The most important factor of anorexia development is the upset balance between hunger and satiation processes. Satiation and hunger centres are stimulated by the orexogenic factors mainly by the neuropeptide Y (NPY) and anorexogenic factors mainly by leptin and also insulin, urocortin, glucagon-like peptide (GLP-1) and α melanocortin (αMSH) [9, 10].

It is proved that in patients with advanced tumours high level of cytokines concentration may mimic the activity of leptins in the hypothalamus stimulating the feeling of satiation, increase the CRF (corticotropin releasing factor) and serotonin secretion and simultaneously inhibit factors connected with NPY such as galanin, MCH (melanin-concentrating hormone), oxerin and opioid peptides. Local tumour interaction and other causes of fast satiation and eating discouraging symptoms (such as nausea, vomits, pain etc.) or psychodepresive disorders (occuring in 20–60% patients with advanced cancer), may significantly influence the appetite [1, 4, 8].

It is worth considering that in most of patients the intensity of anorexia may be inadequatly low in comparison with the degree of the cachexia.

Fast progressing cachexia leads to anaemia, malnutrition, loss of muscle mass and loss of activity, disturbances of internal organs and immune system functions, changes of the appearance, depression, poorer social contacts, worse quality of life, and in the end to the faster death of the patient. In cachexia treatment various drugs are being applied. Positive effects have been proved for: progestagens, glucocorticoids and prokinetics. In some cases adjuvant drugs such as antidepressants, non-steroid anti-inflammatory drugs (NSAID), anabolic steroids and cannabinoids may also have positive action. Participation of following factors: thalidomide, β_2-mimetics, ghrelin, anabolic cytokine analogues, anti-TNFα antibodies, drugs anti-NF$\kappa\beta$, somatotropin/ IGF is still under investigation [2, 7, 10].

Aim of the study

The aim of the study was to establish correlation between the degree of cachexia and diagnosed endocrine disorders which may influence metabolic processes as well as a potential influence of the applied treatment on studied parameters and general status of the patients.

Material and methods

98 patients aged 36–70 years (mean — 55 years) with various degree of cancer cachexia were qualified to the study. Patients with confirmed presence of coexisting acute or exacerbated inflammation, like purulent changes and decubitus etc. were excluded from the study group. All of the patients were able to eat normally. In all patients basic biochemichal tests were performed and chosen hormonal parameters: diurnal cortisol rhythm, thyroid hormones (FT4, FT3, rT3) and thyreotropin level (TSH), insulin level, IGF-1, cytokines levels (IL-6, TNFα). Sex hormones levels were not measured due to the wide range of age of the patients. The investigations were performed with the consent of the patients during routine biochemical blood tests. Symptoms control card was used. It allowed to assess the correlation between other factors (VAS scale pain control, depression and anxiety degree in HADS scale, loss of appetite, nausea, decrease of efficiency in 100-degree Karnofsky scale) which may cause cachexia. The study protocol included information concerning the course of the disease and the latest causative and symptomatic treatment. In the statistical analysis, the Shapiro-Wilk test was used to assess the distribution normality of the tested variables. In case of normal distribution, Student t-test and variance analysis with repeated measurements with Bonferoni test were used. For variables without normal distribution the differences were evaluated with the use of Mann-Whitney test and Friedman test with Dunn test for multiple comparisons. Correlation of variables with normal distribution was tested with the use of Pearson correlation coefficient, in case of other variables — with the use of Spearman correlation coefficient. The hypotheses were verified with the significance level $\alpha = 0.05$.

Patients were divided into four groups:

group I — 25 patients with newly diagnosed advanced cancer and cancer cachexia symptoms (without complex symptomatic treatment);

group II — 25 patients with cancer cachexia treated symptomatically* with non-steroid anti-inflammatory drugs (treated systematically longer than 4 weeks);

group III — 23 patients with cancer cachexia treated symptomatically* with glucocorticoids — dex-

amethasone 4 mg daily (treated systematically longer than 4 weeks);

group IV — 25 patients with cancer cachexia treated symptomatically with progestagens — megestrol 800 mg daily (treated systematically longer than 4 weeks).

*symptomatic treatment means that there existed additional significant (other than cachexia) indications for NSAIDs or glucocorticoids.

The study group included patients with tumours of the abdomen (colorectal cancer, pancreatic cancer, ovarian cancer). In all the groups (I–IV) the distribution of the tumours among the patients was similar. The control group consisted of 30 healthy people.

Results

In the hormonal tests most of the patients presented high cortisol level without diurnal rhythm, disturbances of T4 conversion to T3 (low T3 syndrome) with elevated rT3 levels, low fasting insulin levels and lowered IGF-1 level. TNFα and IL-6 levels were elevated. In the studied group statistically significant positive correlation between body weight loss and loss of apetite ($p < 0.01$), worse pain control ($p < 0.01$), severity of depression ($p < 0.01$), elevated cortisol level ($p < 0.05$) was proved. Treatment efficacy with all drug groups described above (later these drugs were used in combination) was the lowest in patients with low Karnofsky score and with large initial weight loss. Despite the tendency, the weight loss did not correlate statistically significant with TNFα ($p = 0.09$) and IL-6 ($p = 0.06$) levels. Laboratory tests in most of the patients revealed moderate anaemia, moderate hypoproteinaemia, lack of significant electrolite disturbances and glycaemia regulation disorders (tendency to the retardation of postprandial insulin peak and insulin resistance). Elevated cortisol level correlated negatively with the lower performance status in the Karnofsky scale ($r = –0.4$, $p < 0.05$) and positively, with the apetite loss (statistically insignificant; $p = 0.06$, $r = 0.3$). In two patients with fast progression of weight loss hyperthyroidism was diagnosed; high fT4 and fT3 levels and lowered TSH level < 0.05 μU/ml (probably hyperthyroidism was induced by the intake of vitamins preparation with high iodine content). Patients

Table 1. Encompassing results of the study (median values rating)

Parameters (median)	Control group	Group I	Group II	Group III	Group IV
Weight loss					
Last 6 months (%)	0	–20	–22	–20	–23
Last month (%) — during therapy	0	–5	–4	0	+3
Haemoglobinn (12–16 g/dl)	14.2	11.3	10.9	10.6	11.0
TNFα (n. < 12 pg/ml)	10	69	45	33	38
IL-6 (n. < 31 pg/ml)	23	318	235	80	98
Cortisol at 8.00 a.m. (n. 350–650 pmol/l)	472	738	700	215	450
Cortisol (06.00 p.m.) (n. 120–270 pmol/l)	160	522	492	194	288
FT4 (n. 9–21 pmol/l)	15.0	17.0	16.8	13.9	15.1
FT3 (n. 4–8 pmol/l)	6	4.3	4.1	3.9	4.5
rT3 (n. 9–35 ng/dl)	24	58	65	66	62
TSH (n. 0.3–3.5 μU/ml)	1.1	1.8	1.6	1.2	1.5
Anorexia (0–3)	0	1.5	1.5	0.5	0
Pain intensity (VAS 0–10)	0	5	3	2	2
Depression (HADS scale)	3	9	7	6	5
0–7 norm	100%	40%	53%	53%	60%
8–10 border values		20%	20%	20%	20%
11–-21 depression		40%	27%	27%	20%
Anxiety (HADS scale)	3	10	9	7	7
0–7 norm	100%	40%	40%	53%	53%
8–10 border values		20%	20%	20%	21%
11–21 pathologic anxiety		40%	40%	27%	26%
Karnofsky's scale (100–0)	100	50	60	60	60

TNFα — tumor necrosis factor alpha; IL-6 — interleukin 6; FT3 — free triiodothyronine; FT4 — Free Thyroxine; rT3 — reverse triiodothyronine; TSH — thyrotropin; VAS — visual analogue scale; HADS — Hospital Anxiety and Depression Scale

treated with non-steroid anti-inflammatory drugs, glucocorticoids and progestagens in most cases showed increased and statistically significant lower levels of interleukines and TNFα ($p < 0.05$) in comparison to the patient not treated with these drugs. The results are presented in Table 1.

Discussion

The results indicate that cancer cachexia is influenced by many factors among which the endocrine system plays vital role. Chronic stress caused by the cancer causes prolonged activation of subthalamus-pituitary-adrenals axis and impairment of the reflexive inhibition in this axis. This mechanism is similar to the one observed in depressive disorders. Excessive CRF production and excretion, adaptive decrease of ACTH response to the CRF level, decrease of number and sensitivity of glucocorticoid receptors are the effects of aforementioned mechanisms. Persistently decreased CRF level is connected with the low mood, intensification of the anxiety-depressive reaction, sleep and apetite disorders (potential indication for the adjuvant therapy with antidepressants in approximately 40–60% patients) [2–4, 11]. Chronic hypercortisolism causes catabolism of proteins, lipolysis, increased gluconeogenesis. Together with high cytokines levels hypercortisolism induces insulin resistance, causing tendency to postprandial hyperglycaemia inhibiting apetite after intake of small amount of food [12–14]. The results as well as the literature data indicate that use of NSAIDs, glucocorticoids or progestagens, may significantly decrease concentration of cytokines, especially of TNFα that is vital in cachexia. On the one hand TNFα increases secretion of ACTH, on the other activates NF$\kappa\beta$ which inhibits the synthesis of MyoD protein (Myogenic regulatory factor D). MyoD deficiency is a cause of inhibition of formation and diferentiation of muscle tissue which causes musle atrophy and cachexia. To date no effective TNFα inhibiting drug has been developed. It is possible that NF$\kappa\beta$ will be a trigger point for a new generation of drugs [15–18]. Clinical observation indicate that cachexia correlates more with the duration of high cytokines levels than with their sporadically measured absolute values. Degree of production inhibition of IL and TNFα varies between the drugs: it is the highest in case of glucocrticoids, slightly lower for progestagens and the lowest for NSAIDs. An advantage of progestagens lies in their partial resemblance to the glucocorticoids in the anti-inflammatory effect without coexisting significant catabolic effect especially on the muscle tissue observed in case of prolonged administration of dexamethasone [19, 20]. Reduction of cytokine concentration irrespective of the applied treatment decreases their leptin-like inhibitory effect on appetite. Physiological cortisol profile may significantly influence the reduction of depressive disorders tendency. During Megestrole therapy it must be remembered that prolonged high doses administration may permanently inhibit the hypothalamus–pituitary–adrenals axis. Attempting to reduce the disorders causing cancer cachexia, symptomatic treatment must be performed; mainly managing pain, nausea, vomiting and other factors leading to anorexia. Trials of intensive parenteral alimentation, especially if there is a possibility of regular, oral food intake, in most advanced cases are ineffective and sometimes decrease comfort of therapy [21–23]. Cancer cachexia treatment should base on the analysis of different clinical parameters. Pharmacological treatment should aim at the good control of the symptoms and improvement of psychological condition of the patient. Final conclusions of our studies may be modified due to the relatively low number of patients and restricted spectrum of cancer diseases included in the study.

Conlusions

1. Cancer cachexia results from many different factors. One of the most significant factors is partially disordered function of the endocrine system, especially the hypothalamus — pituitary — adrenals axis.
2. The highest efficiency of cancer cachexia treatment is provided by complex therapy with good control of symptoms, progestagens administration (together with other cytokine inhibiting drugs), antidepressant therapy of selected cases.
3. Efficacy of cachexia syndrome therapy decreases with the increase of the disease stage and with the deterioration of the general status.

References

1. Baracos V.E. Cancer-associated cachexia and underlying biological mechanisms. Ann. Rev. Nutr. 2006; 26: 435–461.
2. Muscaritoli M., Bossola M., Aversa Z., Bellantone R., Rossi-Fanelli F. Prevention and treatment of cancer cachexia: new insights into an old problem. Eur. J. Cancer 2006; 42: 31–41.
3. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. Cancer J. Clin. 2002; 52: 5272–5291.
4. Laviano A., Meguid M., Rossi-Fanelli F. Cancer anorexia: clinical implications, pathogenesis and treatment. Lancet Oncol. 2003; 4: 689–694.

5. Strasser F., Bruera E.D. Update on anorexia and cachexia. Hematology/Oncology Clin. North Am. 2002; 16: 589––617.
6. Saini A., Nasser AS., Stewart C.E. Waste management — cytokines, growth factors and cachexia. Cytokine Growth Factor Rev. 2006; 6: 475–486.
7. Argiles J.M., Busquets S., Lopez-Soriano F.J. Cytokines as mediators and targets for cancer cachexia. Cancer Treat Res. 2006; 130: 199–217.
8. Tisdale M.J. Cancer cachexia: metabolic alternations and clinical manifestations. Nutrition 1997; 13: 1–7
9. Bong C., Taylor S., Tisdale M.J., Williams G. Cachexia in MAC16 adenocarcinoma; suppression of hunger despite normal regulation of leptin, insulin and hypothalamic neuropeptide Y. J. Neurochem. 2001; 79: 1004–1012.
10. Mantovani G., Maccio A., Massa E., Madeddu C. Managing cancer-related anorexia-cachexia. Drugs 2001; 61: 499–514.
11. Landowski J. Depression like a chronic stress. Discussion about Depression 2001; 17: 2–6.
12. Yoshikawa T., Noguchi Y., Satoh S et al. Insuline resistance and the alterations of glucose transporter-4 in adipose Wells from cachectic tumor Bering rats. J. Parenter. Enteral. Nutr. 1997; 21: 347–349.
13. Laviano A., Meguid M.M.., Yang Z.J. et al. Cracking the riddle of cancer anorexia. Nutrition 1996; 12: 706–710.
14. Schein P.S., Kisner D., Haller D. et al. Cachexia of malignancy. Potential role of insuline in nutritional management. Cancer 1997; 43: 2070–2076.
15. Hasselgren P., Wray C., Mammen J. Molecular regulation of muscle cachexia: it may be more than the proteasome. Biochem. Biophys. Res. Commun. 2002; 290: 1–10.
16. Coletti D., Yang E., Marazzi G., Sassoon D. TNF? inhibits skeletal myogenesis through a PW1-dependent pathway by recruitment of caspase pathways. EMBO J. 2002; 21: 631–642.
17. Mitch W.E., Price S.R. Transcription factors and muscle cachexia: is there a therapeutic target? Lancet 2001; 357: 734–735.
18. Lorite M.J., Thompson M.G., Drake L.G et al. Mechanism of muscle protein degradation induced by a cancer cachectic factor. Br. J. Cancer 1998; 78: 850–856.
19. Maltoni M., Fabbri L., Nanni et al. Serum levels of tumor necrosis factor alpha and anorexia in cancer patients. Support Care Cancer 1997; 5: 130–135.
20. Loprinzi C.L., Kugler J.W., Sloan J.A. et al. Randomized comparison of megestrol acetate versus dexamethasone versus fluoxymesterone for the treatment of cancer anorexia/cachexia. J. Clin. Oncol. 1999; 17: 3299–3306.
21. Tchekmedyian N.S. Costs and benefits of nutrition support in cancer. Oncology 1995; 9 (11 supl.): 79–84.
22. Mirhosseini N., Fainsinger R.L., Baracos V. Parenteral nutrition in advanced cancer: indications and clinical practice guidelines. J. Palliat. Med. 2005; 5: 914–918.
23. Hutton J.L., Martin L., Field C.J., Wismer W.V., Bruera ED., Watanabe S.M., Baracos VE. Dietary patterns in patients with advanced cancer: implications for anorexia-cachexia therapy. Am. J. Clin. Nutr. 2006; 84: 1163–1170.