POINT OF VIEW

Hormonal treatment in advanced non-small cell lung cancer: fact or fiction?

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Hormonal treatment in advanced non-small cell lung cancer: fact or fiction? J.F. Vansteenkiste, J.P. Simons, E.F. Wouters, M.G. Demedts. ©ERS Journals Ltd 1996.
ABSTRACT: In patients with advanced non-small cell lung cancer, cachexia is an important cause of morbidity and mortality. The pathogenic mechanism of this finding, usually referred to as "cancer anorexia and cachexia syndrome" (CACS), is complex and far from completely understood, but a disturbed equilibrium between possible food intake and metabolic needs seems to be fundamental. The literature data on the treatment options in advanced non-small cell lung cancer (NSCLC) with cachexia are reviewed.

Based on the clinical studies on cancer cachexia, some recommendations for the therapeutic approach of this disorder in patients with advanced NSCLC can be given. Metoclopramide is easily administered, can alleviate gastric disturbances, but probably does not correct the catabolic spiral of CACS. There are not enough data to advise the use of parenteral nutritional support, hydrazine, cyproheptadine, tetrahydrocannabinol or nandrolone decanoate. Corticosteroids are useful in additional analgesia and fast palliation of very weak and debilitated patients in the final episode of their disease. Recent data in non-small cell lung cancer patients are in favour of the use of high-dose progestagens to improve both appetite and weight.
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Metastatic non-small cell lung cancer (NSCLC) has a very poor prognosis, with a median survival of 3–5 months in nonselected patient groups, *e.g.* local cancer registries [1]. Cisplatinum-based combination chemotherapy can give a small but significant survival benefit [2, 3]. Further multicentre studies with new cytotoxic agents in NSCLC are needed to improve the current survival results. In the mean time, clinicians are investigating the role of chemotherapy in symptom control and improvement of quality of life [4, 5].

Beside this, other palliative treatment modalities have been studied in controlled clinical trials. One of the characteristics of patients with advanced NSCLC is the development of progressive weight loss and cachexia. This detrimental evolution is usually referred to as "cancer anorexia and cachexia syndrome" (CACS), in accordance with similar clinical pictures in a range of other malignant processes.

After a short statement on occurrence, pathogenesis and clinical aspects, the different treatment options in NSCLC with so-called CACS are reviewed.

Occurrence of CACS

CACS is an important cause of morbidity and mortality in cancer patients in general [6]. At least half have so-called clinical CACS, a complex abnormal biochemical state, as a result of anorexia, inadequate food intake and inadequate food metabolism, and leading to progressive weight loss and tissue-wasting, poor performance status and, finally, death [7].

There is considerable variation in the occurrence of CACS according to the type of tumour [8]. Major weight loss is rare in breast cancer, sarcoma and some lymphomas. Impressive weight loss can be found in patients with gastrointestinal tumours, especially gastric carcinoma, where food intake is obviously disturbed.

Patients with severe CACS have poorer treatment response and survival [9]. Weight loss is also, besides tumour stage and performance status, a major prognostic factor in NSCLC [10]. Finally, a relationship between weight loss and poor survival has been demonstrated in NSCLC [11].

Pathogenesis of CACS

The pathogenic mechanism of CACS is complex and far from completely understood. An overview of contributing factors is given in table 1. More details on animal models, biochemical and metabolic studies can be found in the recent review by NELSON [12]. The fundamental aspect of weight loss is a disturbed balance between food intake and increased metabolic needs. In NSCLC, in particular, weight loss is related to hypermetabolism [13], resulting in a negative energy balance [14]. The higher metabolic rate could be partially explained by the presence of an inflammatory state [15]. Other reported factors probably inducing an increase in metabolic

Table 1. – Aetiological factors in CACS

Inadequate food intake
Anorexia
  Interleukins
  Psychological factors
  Alterations of taste and smell
  Nausea/vomiting
  Mucositis
  Gastroparesis
  Mucosal atrophy/malabsorption
  Obstruction/ileus
Lack of energy for adequate food intake
Increased metabolic needs
Energy consumption by tumour cells
  Glycosis
  Lactate recycling (Cori cycle)
Increased metabolic rate
Metabolic changes
  Proteins
    Increased breakdown for tumour growth
    Decreased total body protein
    Negative nitrogen balance
    Muscle- and tissue-wasting
  Fats
    Depletion of fat stores
    Impaired use of fat (lipoprotein lipase activity)
  Carbohydrates
    Depletion of glycogen stores
    Insulin resistance/glucose intolerance
    Gluconeogenesis

CACS: cancer anorexia and cachexia syndrome.

needs are tumour growth, with inefficient, and thus very consuming, mechanisms and numerous tumour-induced metabolic disturbances, all causing a less efficient use of nutrient intake. In contrast to starvation, where energy rich fat is used as primary fuel, in patients with CACS a defective fat metabolism (less lipoprotein lipase activity, excess-ive mobilization of triglycerides) is reported. In this sett-ing, glycogen and proteins, in particular, may be used as energy source [16], which results in muscle- and tissue-wasting, and clinically in the initiation of the so-called "cachectic spiral".
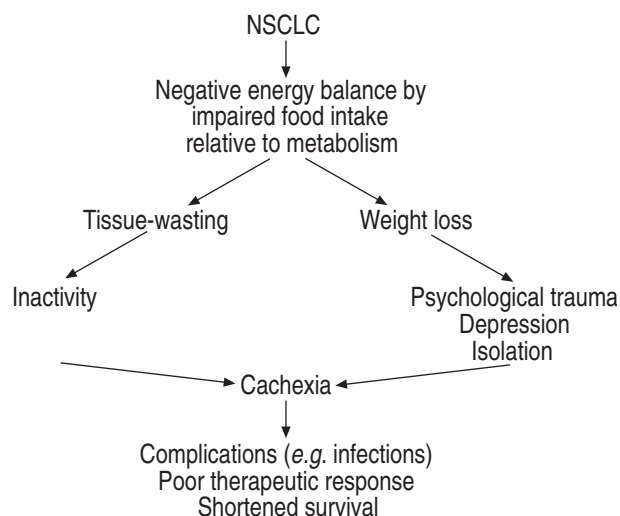
NSCLC

Negative energy balance by
impaired food intake
relative to metabolism

Tissue-wasting   Weight loss

Inactivity   Psychological trauma
        Depression
        Isolation

Cachexia

Complications (*e.g.* infections)
Poor therapeutic response
Shortened survival

Fig. 1. – Clinical picture of cancer cachexia. NSCLC: non-small cell lung cancer.

Clinical picture

The pathogenic mechanisms of CACS bring patients with advanced NSCLC into the so-called "cachectic cir-cle" or "cachectic spiral", schematically depicted in fig-ure 1. Food intake is inadequate to counterbalance the increased metabolic needs, and this negative energy bal-ance will lead to tissue-wasting, clinically manifested by loss of weight. The perception of ongoing weight loss can cause psychological trauma, depression and isola-tion, which in their turn can promote anorexia and dimin-ished food intake. Tissue- and muscle-wasting induce low performance status and inactivity. The end result is cachexia, higher susceptibility to complications such as infections, less optimal response to or increased toxicity of potential anti-cancer treatments [8], and shortened sur-vival [8, 17].

Treatment

Nutritional support

Clinical and biochemical features suggest that nutri-tional support is needed in the presence of weight loss of more than 10% of the initial body weight, or in a sit-uation where an aggressive anticancer treatment can be foreseen [18].

Where parenteral nutrition can be useful in patients scheduled for gastrointestinal cancer surgery, in which mechanical factors impede adequate food intake [19], and in patients treated during short intervals with highly effective chemotherapy, the indication for parenteral nut-ritional support is questionable in NSCLC [11, 20–22]. In as far as energy expenditure in these often hypermeta-bolic patients cannot be balanced by normal food intake, nutritional supplementation, particularly by enteral solu-tions, has to be considered. Taking into account the possi-ble complications (catheter infection, pneumothorax) and the high cost (prolonged hospital stay), parenteral nutri-tional support in CACS can be considered as "oncolog-ically illogical" [23].

Pharmacological agents

Besides the use of specific agents, one must remem-ber to give attention and proper treatment to other aspects contributing to the anorexia, such as pain, mucositis, con-stipation, nausea and depression.

Several placebo-controlled studies in cancer cachexia show that placebo effects can substantially influence the results. Small, uncontrolled clinical studies must, thus, be interpreted with a large amount of caution, and are only mentioned in this review in those instances where no controlled data are available.

In view of the different pathogenic mechanisms con-tributing to tissue-wasting in cancer patients, in many studies data interpretation is hampered by the lack of specification or stratification for type of tumour.

Nonhormonal agents (table 2). Cyproheptadine is an anti-histamine compound with antiserotonergic action, which

Table 2. – Data on the studies with various pharmacological agents in CACS

First author [Ref]	Pts	R	P	Effect on appetite		Effect on weight		Effect on quality of life	
				Total gp*	Subgp*	Total gp	Subgp	Method	Effect
Cyproheptadine studies									
KARDINAL [24]	293	Yes	Yes	NR	p=0.01	NS	NS		NR
Hydrazine studies									
KOSTY [25]	291	Yes	Yes	NR	NR	NS	NS	EORTC-UNC	Negative
CHLEBOWSKI [26]	101	Yes	Yes	NS	p<0.05	NS	p<0.05		NR
CHLEBOWSKI [27]	65	Yes	Yes	NR	NR	NS	NS		NR
Metoclopramide studies									
NELSON [28]	20	No	No	(improved 13/20)		NR	NR		NR
SHIVSHANKAR [29]	10	No	No	(improved 10/10)		NR	NR		NR
Tetrahydrocannabinol studies									
NELSON [30]	19	No	No	(improved 13/19)		NR	NR		NR
Corticosteroid studies									
MOERTEL [31]	116	Yes	Yes	NR	p<0.05	NS	NS	Karnofsky	NS
WILLOX [32]	61	Yes	Yes	NR	p<0.01	NS	NS	VAS	p<0.01
BRUERA [33]	40	Yes	Yes	p<0.05	NR	NS	NS	ECOG	NS
Anabolic steroid studies									
CHLEBOWSKI [34]	37	Yes	No	NR	NR	NS	NS		NR

*: see text for explanation of these groups (gp). CACS: cancer anorexia and cachexia syndrome; Pts: patients; R: randomized; P: placebo-controlled; NR: not reported; NS: not significant at the p=0.05 level; EORTC-UNC: questionnaire from the European Organisation for Research and Treatment of Cancer/University of North-Carolina; VAS: visual analogue scale; ECOG: performance status score of the Eastern Co-operative Oncology Group.

is well-known for its appetite stimulation. KARDINAL *et al.* [24] randomized 293 patients with advanced malignancies and weight loss of at least 2.2 kg between placebo and treatment with cyproheptadine, 8 mg *t.i.d.* Improvement in appetite was noted in 55% of treated patients *versus* 36% in the placebo group (p=0.01). There was no influence on weight loss. Dizziness and sedation were disturbing side-effects.

Hydrazine sulphate was a promising therapeutic possibility. This substance is known to block a gluconeogenetic enzyme of the Cori cycle, a postulated inefficiently hyperactive metabolic pathway in cancer. A controlled trial by CHLEBOWSKI and co-workers [26] on 101 patients with a weight loss of at least 10% of initial body weight showed that 63% of the patients treated with hydrazine sulphate, 60 mg *t.i.d.*, had improved appetite *versus* 25% of placebo group (p<0.05); 83% of the treated group maintained their weight or gained 2.5 kg *versus* 53% in the placebo group (p<0.05). The striking results with placebo were attributed to intensive dietary counselling. In another study by CHLEBOWSKI and co-workers [27], 65 patients with advanced NSCLC treated with cisplatin-based chemotherapy randomly received either hydrazine sulphate 60 mg, *t.i.d.*, or placebo. Dietary counselling was well-balanced between the two groups. Caloric intake and albumin maintenance were better in the hydrazine sulphate group, there were no significant differences in evolution of weight. There was a trend to better survival in the patients treated with hydrazine sulphate, especially if they had a good initial performance status. This was not confirmed in a more recent controlled, large scale study by KOSTY *et al.* [25]. They randomized 291 good-performance patients with advanced NSCLC between standard cisplatin-based chemotherapy or the same plus hydrazine, 60 mg *t.i.d.*, There was no difference in appetite, evolution of weight, quality of life or survival between the groups.

Metoclopramide can improve gastric function in patients with gastroparesis, which is often present in patients with advanced cancer [28]. Data on this compound are limited and consist only of small, noncontrolled series [29, 35]. They show improvement in appetite in some patients with advanced cancer and early satiety treated with metoclopramide, 10 mg *q.i.d.*, There was no effect on weight.

Appetite stimulation was noted when tetrahydrocannabinol was used in the prevention of nausea and vomiting induced by chemotherapy. Limited uncontrolled data also suggest a beneficial effect on appetite in CACS [30].

Adrenal steroids (table 2). Corticosteroids such as dexamethasone or methylprednisolone are often used in advanced cancer patients not eligible for curative treatment. In an early study, the only noteworthy difference was a higher incidence of peptic ulcers on autopsy in the patients treated with corticosteroids [36]. In the double-blind, controlled study by MOERTEL *et al.* [31], dexamethasone, 6 mg·day^{-1}, or placebo was given to patients with far-advanced gastrointestinal adenocarcinoma [33]. Fifty five percent of treated patients experienced better appetite *versus* 26% in the placebo group (p<0.05). There was no beneficial effect on weight. Two studies used a randomized, double-blind, crossover design [32, 33]. The study by BRUERA and co-workers [33] showed an improvement in appetite in the total group: the visual analogue scale for appetite (0–100) improved from 26±10 to 40±15 (p<0.05). No advantage in weight could be seen. Interestingly, the visual analogue scale for pain decreased from 58±15 to 37±14 (p<0.01), showing a supplementary effect of corticosteroids in (co-)analgesia. None of these studies demonstrated any advantage in performance status measured by Karnofsky or Eastern Co-operative Oncology Group (ECOG) scores. On the contrary, one could expect the opposite, when considering the multiple disadvantages of long-term corticosteroids: peptic ulcers, disturbed

Table 3. – Data on the studies with high-dose progestagens in CACS

First author [Ref]	Pts	R	P	Daily dose* mg	Duration weeks	Effect on appetite		Effect on weight		Effect on quality of life	
						Total gp#	Subgp#	Total gp#	Subgp	Method	Effect
MA studies											
Feliu [38]	150	Yes	Yes	240	8	NS	p=0.001	NS	p=0.01	Karnofsky	NS
Loprinzi [39]	133	Yes	Yes	800	7†	NS	p=0.003	NS	p=0.003		NR
Tchekmedyian [40]	89	Yes	Yes	1600	4	NS	p=0.02	NS	NS	VAS	NS
Schmoll [41]	55	Yes	Yes	480–960	4–8	NS	NS	NS	NS		NR
Bruera [42]	40	Yes	Yes	480	1	p=0.02	NR	p=0.03	NR	Questionnaire	NS
MPA											
Simons [43]	206	Yes	Yes	1000	12	p=0.01	NR	p=0.04	NR	EORTC	NS
Niiranen [44]	89	Yes	No	180$	24	NS	p=0.02	NS	p=0.03		NR
Downer [45]	60	Yes	Yes	300	6	(p<0.01)‡	NR	NS	NS	Karnofsky	NS

*: a daily dose of 160 mg megestrol acetate is equivalent to 1,000 mg MPA; #: see text for explanation of these groups; †: median duration of follow-up; $: average daily dose (calculated from weekly *i.m.* dose); ‡: significant difference between appetite before and after treatment within the MPA group. MA: megestrol acetate; MPA: medroxyprogesterone acetate. For further definitions see legend to table 2.

glucose metabolism, bone loss, fluid retention and proximal myopathy, with decreased muscle strength.

Anabolic steroids, such as nandrolone decanoate, improve the nitrogen balance and could help to preserve total body protein in cancer patients [37]. In a randomized study with only 37 inoperable NSCLC patients, nandrolone decanoate, 200 mg·week^{-1} *i.m.* for 4 weeks, was compared to no additional therapy [34]. Appetite was not scored. There was a nonsignificant trend towards less weight loss in the treated group. Solid conclusions are hampered by the small number and the short follow-up. However, longer use of this high dose would probably result in important side-effects.

Progestagens (table 3). Progestagens have been used extensively in the treatment of hormone sensitive breast cancer [46]. In early studies with high dose, one of the remarkable findings was the improvement in appetite and weight in patients with non-hormone sensitive or non-responding breast tumours. Further studies in other solid tumours were initiated.

Megestrol acetate (MA) was studied in three North-American and two European randomized, controlled trials. Patients with incurable, non-hormone sensitive cancer and varying weight loss (usually 5–10% of initial body weight) were included. One study was too small to draw any meaningful conclusions [41]. Of the four remaining MA studies, Bruera and co-workers [42], using a cross-over design with a treatment duration of 1 week, found a statistically significant beneficial effect for appetite (scored on a visual analogue scale from 0 to 100, average improvement of +15 points in the treated group *versus* average loss of -12 points in the placebo group; p=0.02), caloric intake, weight (average gain +0.2 kg *versus* average loss -0.8 kg, p=0.03), triceps skinfold thickness and subjective energy level. The clinical significance of these findings is, however, unclear given the very short follow-up. The other three studies [38–40] showed a significant beneficial effect of MA on appetite. Two of these studies also found that the subgroup of patients with weight gain was significantly larger in the MA arm than in the placebo arm: Loprinzi *et al.* [39] found a favourable effect on weight (defined as an increase of at least 15 lb) in 16% of the MA-treated patients *versus*

2% in the placebo-group; Feliu *et al.* [38] observed a weight gain of at least 2 kg in 32% of the MA-treated patients *versus* 8% in the placebo group. Quality-of-life was looked at in three studies, no significant beneficial influence of MA was documented.

Medroxyprogesterone acetate (MPA) was used in three randomized European studies. In the British study by Downer *et al.* [45], 60 patients with advanced malignancy, usually lung cancer, were randomized between MPA, 100 mg *t.i.d.*, or placebo. The visual analogue scores for appetite (0–100) of the MPA-treated patients significantly improved during the study interval, data on comparison with the placebo-treated patients were not mentioned. No effect on weight or Karnofsky performance status was shown. Unfortunately, this study suffered from a lack of power (as a result of the relatively small number of 60 randomized patients, in combination with a drop-out rate of over 50% at the end of the 6 week treatment period), impeding the interpretation of its results.

A Finnish study by Niiranen *et al.* [44] randomized elderly lung cancer patients between a treatment with either chemotherapy or chemotherapy and MPA *i.m.* for 6 months. This study was not placebo-controlled. It was revealed that a subgroup of 37% experienced better appetite in the MPA-treated group *versus* 14% in the others (p=0.02); corresponding figures for weight gain were 27 *versus* 7% (p=0.03).

In the Dutch-Belgian trial by Simons *et al.* [43], 206 patients with advanced, non-hormone sensitive cancer, predominantly lung cancer, were randomized between MPA, 500 mg *b.i.d.*, or placebo. Concomitant chemotherapy was allowed, but used in only 12% of patients in both study groups. Primary end-points were appetite (visual analogue scale 0–10), weight and quality of life (European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 (EORTC-QLQ-C30) [47]). Both appetite and weight were significantly better in the entire group of MPA-patients *versus* those with placebo. After 12 weeks, appetite showed a +0.8 increase for MPA and -0.6 decrease for placebo (p=0.01). Data for weight were +0.6 kg for MPA and -1.4 kg for placebo (p=0.04). Patients with oedema were excluded in the weight analysis in order to guarantee the solidity. Improvement in Karnofsky performance status approached

significance after 6 weeks (p=0.07). No benefit in quality of life could be demonstrated by the EORTC-questionnaire. As in other studies, the possible side-effects of MPA (especially thrombosis, diabetes, fluid retention and hypertension) were mild; only fluid retention was somewhat more pronounced in the MPA group when compared with placebo.

SIMONS and co-workers [48] also analysed energy intake and body composition in a subgroup of patients participating in the multicentre trial. Compared to the placebo group, the MPA-treated patients showed a significant increase in energy intake of more than 400 kcal·day^{-1}. Body composition analysis revealed that the induced weight changes (mean difference in weight change between the two groups of 3.0 kg in favour of MPA) could be attributed almost completely to changes in fat mass, fluid retention being of negligible importance.

Conclusion

Based on the clinical studies on cancer cachexia, some recommendations for the therapeutic approach of this disorder in patients with advanced NSCLC can be given. Metoclopramide is easily administered and has a low cost. It can alleviate gastric disturbances, but it is unlikely that this drug would correct the catabolic spiral of CACS. Further controlled data are needed to determine its role precisely.

There are not enough data to advise the use of parenteral nutritional support, hydrazine, cyproheptadine, tetrahydrocannabinol or nandrolone decanoate.

Corticosteroids are useful in cases where additional analgesia is required, and for fast palliation of very weak and debilitated patients in the final episode of their disease. In other instances, they should be avoided for their multiple disadvantages.

In non-small cell lung cancer patients data of reported studies are in favour of the use of high-dose progestagens to improve both appetite and weight. The cost of this treatment, however, warrants further confirmatory evidence, especially on quality of life issues. In the meanwhile, we think that the current data allow us to suggest that palliative hormonal treatment of non-small cell lung cancer patients with cachexia is becoming more than fiction.

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