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Adjuvant treatment for cancer pre-cachexia with vitamins, royal jelly, pollen and cod liver oil: a retrospective, non-comparative clinical study

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Abstract

Cancer anorexia-cachexia syndrome is a multifactorial syndrome characterized by a progressive loss of muscle mass, with or without loss of fat mass, with progressive functional damage, negative protein and energy balance, both caused by reduced caloric intake and metabolic changes.

It is important to recognise precachexia to avoid full-blown

and refractory cachexia. The experience gained by the Working Group of the Hospice Kairos with supplement containing vitamin A, vitamin D, pollen, freeze-dried royal jelly and cod liver oil confirms its usefulness in patients with precachexia. In fact, during the observational period, there was a statistically significant increase in appetite with an improvement of patients' quality of life and a slowdown in progression from precachexia to full-blown cachexia.

Adjuvant treatment for cancer pre-cachexia with vitamins, royal jelly, pollen and cod liver oil: a retrospective, non-comparative clinical study

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Introduction

Anorexia-cachexia syndrome (1-5) is very frequent in patients with chronic progressive diseases (Tab. I).

Table I. Prevalence of anorexia-cachexia syndrome.

Advanced cancers	40-80%	Laviano et al. 2005 Fearon et al. 2011
Heart failure	16%	Anker et al. 1997
Chronic obstructive pulmonary disease	25-33%	Congleton et al. 1999
Renal failure	40%	Kalantar-Zadeh et al. 2003

Cachexia is a common manifestation of seriously sick people, with all the physical, psychological, social, family and existential consequences that this condition entails. This syndrome is usually irreversible, increasing family sense of helplessness and the feeling of inadequacy experienced by the healthcare staff. Tackling anorexia-cachexia syndrome is particularly challenging because it goes against common sense features standing in contrast to paradigms such as the associations among food and life, health, strength, recovery from illness, happiness, celebration, distraction. Hesiod writes that the gods feed themselves with honey and ambrosia because they are powerful and still today food is often associated with a privileged social status and opulence. Paradoxically, our society also transformed food into a cause of illnesses: obesity, anorexia, bulimia sometimes are a real existential "calvary".

Post-modernism leads to another view which is substantial for those who, as the working group at Hospice Kairos of Syracuse, deal with supportive therapies and palliative

care for patients with incurable diseases. The consumer society gives higher value to superfluous, hedonism and pleasure denying suffering and death. Food and its representations are powerful allies to this vision, you just need to observe how much attention the mass media give to food and cooking.

Food, pleasure and life are the antithesis of anorexia, suffering and death. Therefore anorexia-cachexia syndrome is much more than a complex metabolic disorder: it often becomes the corporeal manifestation of suffering and, while facing that suffering, it is difficult to act coherently, thus running the risk of getting into a state of loss and abandonment.

Definition and pathophysiology of cancer anorexia-cachexia syndrome

Cancer anorexia-cachexia syndrome is a multifactorial syndrome characterized by a progressive loss of muscle mass, with or without loss of fat mass, that cannot be completely corrected only with the help of standard nutritional support, thus leading to progressive functional impairment. Its pathophysiology is characterised by a negative protein and energy balance caused by reduced food intake and abnormal metabolism (6,7). The most common metabolic changes in cancer anorexia-cachexia syndrome are:

- increased resting energy expenditure;
- loss of muscle mass as a result of enhanced proteolysis and decreased protein synthesis;
- loss of fat mass and increased lipolysis due to augmented gluconeogenesis with reduced intake of energy substrate, following symptoms such as anorexia, nausea and vomiting;

- insufficient use of newly formed glucose due to hypoinsulinemia and/or peripheral insulin resistance;
- oxidative stress, resulting in damage to DNA, membrane lipoproteins, enzymes and coenzymes that play a central role in the regulation of the main metabolic and cellular pathways.

The release of the proteolysis-inducing factor (PIF), produced by some tumors, seems to be one of the key events in the initiation of cachectic processes. Another central role is played by pro-inflammatory cytokines (IL-1, IL-6, TNF- α), produced both by cancer cell and by the immune system which trigger inflammatory responses that rapidly tend to chronicize.

The same cytokines cause, over time, hypothalamic central signals dysregulation, thus contributing to alterations leading to a neuropeptide Y-induced orexigenic effect inhibition, to an increase in corticotropin-releasing factor (CRF) and in melanocortin-releasing hormone, and to an alteration in ghrelin and cholecystochinin secretion.

A further, certainly central element in the activation and maintenance of cachectic syndrome is leptin, a hormone secreted by the adipose tissue and a central mediator of energy metabolism control. It plays an important role in stimulating adaptive response to cachexia. Weight loss results in a reduction in leptin levels, which, in disease's advanced stages, are, at the same time, inversely related to the severity of chronic inflammation associated with cachexia.

Cancer anorexia-cachexia syndrome should be suspected in patients with:

- severe, incurable disease;
- unintentional weight loss, more than 5% of standard weight, over a period of 6 months;
- weight loss >2% in a patient with BMI <20 or in a patient diagnosed with sarcopenia.

It is very important to adopt adequate assessment tools and follow-up interventions, so as to identify pre-cachexia and to prevent or delay the onset of full-blown and refractory cachexia (8-10). Indeed, in full-blown cachexia weight loss and chronic inflammation have already triggered cyclical reinforcing mechanisms. This event tends to create a domino effect that leads to refractory cachexia characterized by weight loss, clear performance status impairment and lower life expectancy (11-13). Often, in similar frameworks, the use of nutritional supplements is associated with an unfavourable balance between potential risks and undefined clinical benefits.

Given the challenges faced by caregivers and family members after cachexia syndrome onset, it is essential to focus on pre-cachexia.

Family members, unaware of patient's real needs, tend to force him or her to eat enough to risk real relational crises and, above all, preventing even further appropriate dietary counselling (14,15).

Clinical experience

A project, supported by the available scientific literature, has been underway in the Palliative Care Unit at the Hospice Kairos for about two years now. This project involved both people suffering from incurable cancers and their family members as well as people with chronic-progressive non-cancer diseases, who have become increasingly resistant to drug treatments and, presumably, with life expectancy below one year.

Experience gained allows the prediction of disease progression on the basis of some signs and symptoms. On this basis, considerable attention has been paid to pre-cachexia stages, by identifying them early and implementing therapeutic measures deemed effective, even if with different levels of evidence.

The adopted approach enabled to define two pathways.

A screening pathway which included:

- weight assessment and its variations in time;
- Body Mass Index calculation;
- lean body mass assessment, when possible.

A pathway characterized by early assessment of some parameters such as:

- measurement of catabolic and inflammatory mediators (valuation of C-reactive protein, CRP);
- appetite variations and dietary intake, measured using Numerical Rating Scale (NRS);
- functional capacity evaluation (muscular strength);
- quality-of-life assessment.

On the basis of the informations gathered, a presumed diagnosis of pre-cachexia led the Hospice working group to a subsequent multimodal intervention based on:

- dietary counselling;
- management of concomitant symptoms;
- anti-inflammatory drug use;
- administration of dietary supplements;
- possible administration of medroxyprogesterone acetate or megestrol acetate.

Dietary counselling is based on the implementation of a personalised diet plan, reflecting patient's preferences, which is reevaluated on a weekly basis.

The management of concomitant symptoms, in particular those of the digestive system, is an important adjuvant action. The administration of anti-inflammatory drugs, especially low-dose corticosteroids, for a limited period of time (16-18) or, in some selected cases, of COX-2 selective non-steroidal anti-inflammatory drugs (19-21), appears to be effective because it inhibits pro-inflammatory mechanisms. Furthermore, over the last two years now, the Hospice Kairos working group has been focusing on the use of complex dietary supplements, branched chain amino acids and eicosapentaenoic acid (EPA), in the modulation of immunoflogosis, PIF and because of their orexigenic actions (22-24).

Based on the experience gained over these years, we think that the assumption of supplements in patients with pre-cachexia can, at least, delay use of effective drugs such as medroxyprogesterone acetate or megestrol acetate (25-29) which, nevertheless, can cause, sometimes, serious side effects, such as venous thromboembolism. Among supplements taken into consideration, there is a formula including cod liver oil, vitamin A, vitamin D, pollen and lyophilized royal jelly (Liovital AD®, Pharma Line, Milan).

- Cod liver oil is a source of fat-soluble vitamins and omega 3 polyunsaturated fatty acids. Given the anti-inflammatory, anti-angiogenic and anti-proliferative action of these nutrients, some authors argue that their synergy has a preventive and healing effect with respect to the development of multiple diseases (30,31). Studies conducted on the fatty acids contained in cod liver oil suggest that they can be used to prevent some cancer complications, including cancer cachexia (32). Vitamin A plays an important role in reducing free radicals formation, in protecting cellular structures and in maintaining muscle fibre homeostasis (33). The most recent scientific literature shows that, in various conditions, including cachexia, there is a correlation between low blood levels of vitamin D and muscle metabolism disorders. Moreover, some studies show the essential role of vitamin D receptors in maintaining or restoring the muscle health. Finally, several clinical studies emphasise the crucial role that vitamin D supplementation plays in maintaining patient's general health condition and, in particular, in ensuring normal muscle tissues metabolism (34).
- Pollen is useful in patients with anorexia-cachexia because it is considered as an appetite stimulant in addition to improving muscular performances. It is well-known, in fact, that it contains several ingredients essential for muscle fibres metabolism and overall body metabolism (35).

- Royal jelly is rich in essential amino acids, vitamins and minerals and it has anti-inflammatory and antioxidant properties. The scientific literature shows the benefits of royal jelly in counteracting muscle fatigue and anorexia, improving quality of life, even in patients with cancer (36).

Materials and methods

We conducted a retrospective non-comparative clinical study to investigate the benefits of composite dietary supplement in improving appetite and quality of life among patients with pre-cachexia.

Between January and December 2018, 33 patients, 23 men and 10 women were treated. The average age was 65 for men and 63 for women. All treated patients had cancers refractory to specific treatment. In particular, 8 patients (all male) had pancreatic adenocarcinoma, 8 patients (all male) had gastric adenocarcinoma, 10 patients (7 male; 3 female) had lung cancer and 7 patients (all female) had breast cancer (Tab. II).

Table II. Cancer types diagnosed and their sex-based distribution pattern.

	Pancreatic adenocarcinoma	Gastric adenocarcinoma	Lung cancer	Breast cancer
Female	-	-	3	7
Male	8	8	7	-

All patients were diagnosed with pre-cachexia and they started treatment with oral composite dietary supplement (a single-dose reconstituted vial per day) containing vitamin A, vitamin D, pollen, lyophilised royal jelly and cod liver oil (Liovital AD®) (Tab. III). Treatment was based on the assumption of a single-dose reconstituted vial per day, for 60 consecutive days.

Tabella III. Qualitative and quantitative composition of the supplement given to patients. The reported dose for each component refers to the content of one vial (Liovital AD®, Pharma Line, Milano).

Ingredient	Dose
Vitamin A	1,200 µg
Vitamin D	12.5 µg (500 UI)
Lyophilized royal jelly	65 mg
Pollen	30 mg
Cod liver oil	40 mg

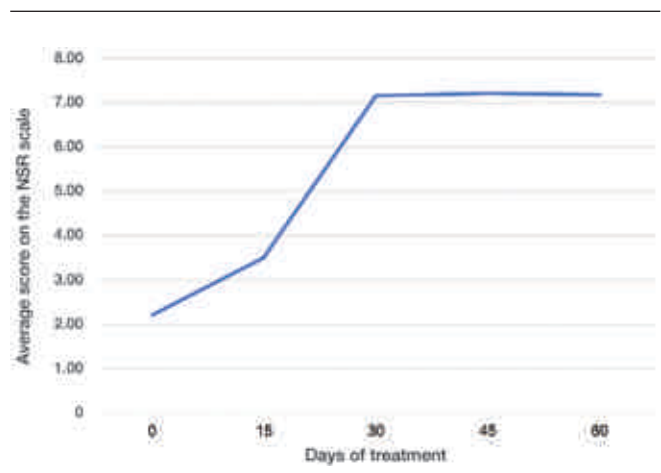
Results

During the 60 days treatment with the dietary supplement, the mean increase in values obtained with NRS was of 4 points (from 2-4= poor appetite to 6-8=good appetite). In particular, the mean NSR score on day 0 of treatment was 2.21, while on day 15 it reached 3.51, and on day 30 the mean value was 7.15. We can state that the best benefit from treatment was achieved on day 30, as the mean NSR scores stayed the same at the subsequent two follow-up visits: indeed, on day 45 the mean

Table IV. NSR score for each patient treated, during the 60 days treatment.

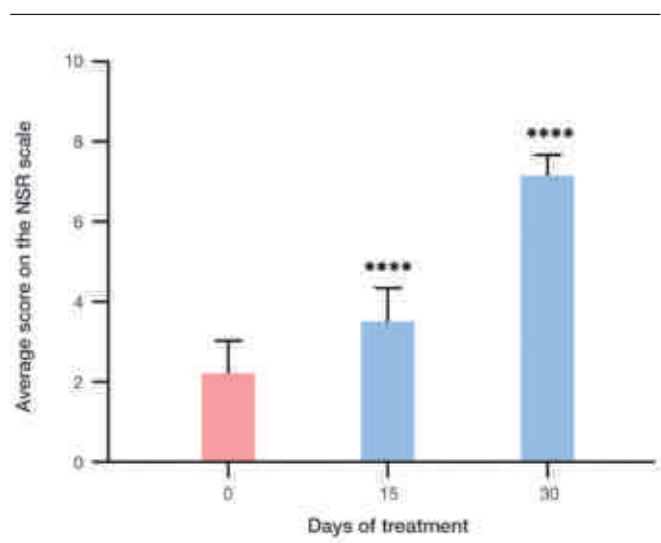
Patient	Number of days of treatment and NSR score				
	0	15	30	45	60
1-AA	2	4	7	7	7
2-MC	3	5	7	7	7
3-GB	2	4	8	8	8
4-RT	2	5	6	7	7
5-GP	3	3	7	7	7
6-DB	0	4	6	6	6
7-RR	2	4	7	7	7
8-FC	3	2	7	7	7
9-DC	2	2	7	7	7
10-GC	2	3	7	7	7
11-LC	3	2	8	8	7
12-MP	4	3	7	7	7
13-GT	2	3	8	8	8
14-FT	3	2	7	7	7
15-GM	3	3	7	7	7
16-SN	3	4	7	7	7
17-NR	2	4	8	8	8
18-ED	3	4	7	7	7
19-AD	1	3	7	7	7
20-LZ	2	5	7	7	7
21-PZ	2	4	8	8	8
22-AL	2	3	7	8	7
23-RB	1	3	7	7	8
24-PT	3	4	7	7	7
25-NG	2	4	7	7	7
26-FG	1	4	8	7	7
27-SO	1	3	7	7	7
28-DR	2	4	7	7	7
29-GP	2	3	7	7	7
30-AT	3	4	7	7	7
31-SR	3	4	8	8	8
32-RC	2	3	7	7	7
33-GM	2	4	7	7	7

Figure 1. Mean NSR score trend in the days of treatment, from the beginning (0) to the end of the study period (day 60). Data are expressed in terms of mean NSR scores calculated from patients-reported scores.



value was 7.21 and on day 60 it was 7.18 (Tab. IV, Fig. 1). Increase in appetite was statistically significant in the first 30 days of treatment ($p < 0.0001$) (Fig 2). The highest mean score stayed the same for almost all patients for approximately 60 days. Subsequently, NSR reached a score of zero concurrently with patients deterioration and with the gradual reduction in life expectancy. Weight gain was moderate, an average of 1 kg (data not reported) over the study period. No patient had weight-loss in the first 30 days of treatment.

Figure 2. Comparison between mean NSR scores at day 0, after 15 days and after 30 days of treatment. VARIATIONS from day 0 to day 15 and from day 15 to day 30 of treatment are statistically SIGNIFICANT, with $p < 0.0001$ in both cases. Data are expressed in terms of NSR mean scores \pm SD for all patients treated ($****p < 0.0001$).



Patients confirmed quality of life improvements with respect to rediscovery of the pleasures of eating. After the first 60 days of treatment, 24 patients (14 men and 10 women) were treated with medroxyprogesterone acetate (single dose of 320 mg/day), confirming the results already highlighted in the literature. The remaining 9 patients showed more clear evidence of deterioration due to cancer progression and died a few days or a few weeks after the last follow-up.

Conclusions

Cancer anorexia-cachexia syndrome has a complex pathophysiology, hence it is difficult to treat. For this reason, pharmacological treatment is often unsuccessful, especially when it is not started within an adequate timeframe.

At the same time, social-family imaginary and the differences between healthy and sick people needs lead to frequent deviations. A consolatory approach based on artificial and enteral nutrition poses deontological dilemmas, in particular

in patients with life expectancy lower than 4 weeks. Discussions on equal distribution of resources and justice highlight the inadequacy of supplementary medical actions not in line with the real possibilities and conditions of the sick person.

The preferred strategy to manage and monitor cachexia is based on early diagnosis and multimodal approach used as progressive pharmacological support. Early detection of pre-cachexia and the use of supplements including ingredients of proven efficacy, also supported by the available scientific literature, are essential to a good medical practice in treating a sick person.

The experience gained by the Working Group of the Hospice Kairos with supplement containing Vitamin A, Vitamin D, pollen, freeze-dried royal jelly and cod liver oil (Liovital AD[®], Pharma Line) confirms its usefulness in patients with pre-cachexia. In fact, during the observational period, there was a statistically significant increase in appetite with an improvement of patients' quality of life and a slowdown in progression from pre-cachexia to full-blown cachexia. It would be advisable to acquire deeper knowledges to improve quality of life of people with incurable disease.

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Vitamin A	1200 mcg	150
Vitamin D	12,5 mcg 500 UI	250
Pollen dry extract	30 mg	
Freeze-dried royal jelly	65 mg	
Cod liver oil dry extract	40 mg	
Glycine	300 mg	



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