Purpose of review
Significant achievements have been obtained in cancer treatment, but the clinical relevance of drug
approach in daily practice remains questionable due to the high costs, limited efficacy, and negligible
influence on quality of life. A new concept is emerging which is based on the early combination
of chemotherapy and nutrition therapy.

Recent findings
Inflammation dictates tumour initiation, progression and growth. Omega-3 fatty acids exert anti-
inflammatory effects, and therefore recent studies investigated their role in cancer prevention, in cancer
cachexia treatment and in enhancement of antitumour therapies. Limited evidence suggests a role for
omega-3 fatty acid supplementation in cancer prevention, but they have been shown to preserve muscle
mass and function in cancer patients even during active treatment. During chemotherapy, omega-3 fatty
acids may contribute to a reduced inflammatory response, but whether cancer treatment toxicity can be
prevented remains to be assessed. Finally, small studies showed that omega-3 fatty acids increase response
rate to chemotherapy.

Summary
Combination of chemotherapy and omega-3 supplementation appears an effective strategy to enhance the
clinical outcome of cancer patients in their curative and palliative clinical trajectory.

Keywords
cachexia, DHA, EPA, response rate, toxicity

INTRODUCTION
During the past decade, better understanding of the
mechanisms of carcinogenesis, cancer progression
and resistance to treatment has been achieved. Therefore, it is not surprising that the incidence
rates of many cancers and the relative risk of cancer
death are both declining [1]. Nevertheless, the
current drug approach to cancer is disappointing
since it delivers statistically significant results,
whose clinical relevance is questionable due to high
costs, suboptimal response rate, increased toxicity
and negligible impact on quality of life [2,3]. It is therefore becoming imperative to integrate
traditional therapies with new concepts, which
may enhance their efficacy, ideally at a fraction of
the financial costs currently needed.

A promising concept is combination of drugs
targeting cancer cells with strategies supporting the
host or priming his/her metabolism. Indeed, in daily
clinical practice cancer cells do not exist per se,
rather patients with cancer. Therefore, any effective
therapeutic strategy should target the cancer while
simultaneously supporting the host [4]. Preliminary
observations showed that integrating supportive
care, that is, psychological support, nutritional care
and pain control, during active treatment in lung
cancer patients resulted in reduced distress and
enhanced survival [5]. It is therefore tempting to
speculate that specific nutrients given at specific
doses and at critical time points in the clinical
journey of cancer patients may increase response
rate to treatment and improve patient centred
outcomes.

OMEGA-3 FATTY ACIDS AND CANCER
PREVENTION
Among the many nutrients with metabolic effects
potentially relevant to cancer patients, polyunsatu-
rated omega-3 fatty acids received intense attention

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by clinicians and epidemiologists since the late 1980s. Omega-3 fatty acids are mainly derived from fish oil, and are characterized by the presence of a double bond on the third carbon atom from the methyl end of the carbon chain (omega end). The omega-3 fatty acids with clinically relevant effects in the oncology setting are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and α-linolenic acid (ALA), due to their anti-inflammatory effects.

Omega-3 fatty acids, and in particular EPA, are metabolized by the same enzymes, that is, lipoxygenase and cyclooxygenase, which metabolize polyunsaturated omega-6 fatty acids, including arachidonic acid. However, the mediators of inflammation, that is, thromboxanes and prostaglandins, deriving from arachidonic acid, exert greater inflammatory activity when compared with the mediators deriving from EPA. Therefore, a diet rich in EPA would negatively modulate the inflammatory cascade [6**]. Considering the impact of inflammation on the initiation and progression of cancer cells [7], a diet rich in omega-3 fatty acids may protect from cancer, at least at certain sites [8*].

Gerber [9*] has recently reviewed prospective and case-control observational studies investigating the possible protective effects of the dietary intake of omega-3 fatty acids on cancer development. Available evidence seems to suggest that ALA per se is neither a risk factor nor a beneficial factor for cancers. Interestingly, only observational studies on colorectal, prostate and breast cancers showed limited evidence on the possible role of omega-3 fatty acids in cancer prevention because insufficient homogeneity of the observations [9*]. Indeed, epidemiological studies suffer from heterogeneity due to inherent difficulties (i.e. confounding and dietary pattern context, measurement error, level of intake, genetic polymorphisms); nevertheless it appears that cancer prevention cannot be attributed to a single nutrient, but other factors, including genetic background and lifestyle, play an important role as well. This may explain why intervention studies involving single nutrients frequently failed to prevent chronic diseases [10].

**OMEGA-3 FATTY ACIDS AND CANCER CACHEXIA**

Progressive and irreversible deterioration of nutritional status, that is, cachexia, is a frequent complication of tumour growth. Unlike starvation-induced malnutrition, cancer cachexia is not reversed by standard nutritional support since cachexia results from the combination of anorexia, reduced food intake and profound metabolic changes which are responsible for the onset of anabolic resistance [11**]. The main characteristic of cancer cachexia is the progressive loss of muscle mass [11**] leading to sarcopenia, which in turn translates into clinically relevant negative consequences. Liefers et al. [12*] have recently observed in 234 colorectal cancer patients undergoing surgery that the prevalence of sarcopenia is approximately 38%. More importantly, infection risk was greater (23.7 vs. 12.5%) and length of hospital stay was longer (15.9 vs. 12.3 days) for sarcopenic patients overall, especially for those older than 65 years [12*]. In a multivariate model in patients older than 65 years, sarcopenia was an independent predictor of both infection and rehabilitation care [12*]. Similarly, Parsons et al. [13*] showed in advanced cancer patients that the majority of them are overweight and sarcopenic. Interestingly, sarcopenia reduced expected survival, irrespectively of patients’ BMI [13*]. Finally, Prado et al. [14] showed in patients with solid tumours that the presence of sarcopenic obesity was associated with poorer functional status compared with obese patients who did not have sarcopenia, and independently predicted survival.

Inflammatory cytokines play a significant role in the pathogenesis of cancer cachexia [15]. Consequently, the anti-inflammatory effects of omega-3 fatty acids may be of benefit in the prevention and treatment of cancer cachexia. Ries et al. [16*] systematically reviewed 38 papers testing this hypothesis. In general, smaller trials reported a good effect of
omega-3 fatty acids in patients with advanced cancer and cachexia [16*]. However, larger randomized controlled trials could not support the positive results, as they mostly did not find a significant effect [16*]. Similar conclusions were reported by van der Meij et al. [17**] who systematically reviewed omega-3 fatty acid trials in cancer patients. Some benefits were found for oral supplementation of omega-3 fatty acids on body weight (but not on lean body mass) and quality of life in cancer patients during chemo-radiotherapy and in palliative care [17**]. Effects on Karnofsky Performance Status and survival were inconsistent [17**].

Available data are insufficient to draw any robust recommendation for the use of omega-3 fatty acids in the prevention/treatment of cancer cachexia since available clinical studies are highly heterogeneous (Table 1). Also, the number of cancer patients involved in these trials is generally limited, making it difficult to generalize the results obtained to the whole oncologic population. Therefore, the many confounding elements still permeating this research field may contribute to the lack of robust evidence. Indeed, when well designed although small clinical trials are considered (i.e. homogeneous patients not yet in the refractory phase of cachexia, stratified in active and control groups, supplemented with enough dose of omega-3 fatty acids on top of energy and protein requirements), then the results appear promising [18*]. Indeed, van der Meij et al. have recently studied 40 lung cancer patients receiving multimodality treatment [19*]. Patients were then stratified to receive an EPA-enriched oral nutritional supplement (n = 20) or an isocaloric standard supplement for 5 weeks. Results show that EPA-supplemented patients improved quality of life and functional status when compared to the control group [19*]. Similar results were obtained by Murphy et al. [20*] who studied 40 lung cancer patients receiving active treatment. Patients were invited to take fish oil supplementation (i.e. 2.5 g EPA + DHA/day) during chemotherapy. After approximately 10 weeks, patients in the control group (n = 24) experienced an average weight loss of 2.3 kg, whereas patients receiving fish oil maintained their weight [20*]. Patients with the greatest increase in plasma EPA concentration after fish oil supplementation were found to have the greatest gains in muscle [20*]. Approximately 69% of patients in the fish oil group gained or maintained muscle mass. Comparatively, only 29% of patients in the control group maintained muscle mass, and overall the control group lost 1 kg of muscle [20*]. Weed et al. [21] investigated in 31 head and neck cancer patients the effects of the perioperative supplementation of an EPA-enriched oral nutritional supplement on lean body mass. The results obtained show that this perioperative nutritional intervention, started not later than 2 weeks prior to surgery, was associated with a 3.2 kg gain in lean body mass [21]. Although interesting, the clinical relevance of this study is limited by the lack

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Lipid metabolism and therapy

of a control group. It is therefore mandatory that a more global consensus is reached among researchers on key standards to be used in clinical trials on cancer cachexia.

OMEGA-3 FATTY ACIDS AND CANCER TREATMENT TOXICITY

The development of haematological, gastrointestinal or dermatological toxicities during or soon after completion of anticancer therapies compromises the delivery of adequate treatment to cancer patients and jeopardizes their chances to obtain clinical benefits [22]. Consistent evidence demonstrate that dose-limiting toxicity in cancer patients is related to sarcopenia [23,24]. Considering the role of omega-3 fatty acids in preserving/restoring muscle mass in cancer patients, it could be hypothesized that fish oil supplementation may reduce chemotherapy associated toxicity by improving lean body mass.

Murphy et al. [25] studied 46 lung cancer patients receiving first-line chemotherapy, who were invited to consume 2.5 g EPA+DHA/day. After approximately 10 weeks of supplementation, no difference in the incidence of dose-limiting toxicity was observed between patients receiving fish oil (n=15) and nonsupplemented patients (n=31) [25]. A finding of note was that supplemented patients significantly increased their muscle mass when compared to controls [20]. Machon et al. [26] orally supplemented 31 head and neck cancer patients for 5 days before each cycle of chemotherapy with an enriched formula, containing 3 g EPA+DHA/day, immune enhancing amino acids and a mix of antioxidant vitamins and micronutrients. At baseline, levels of inflammatory, pro-angiogenic and pro-oxidative stress markers were increased, but inflammatory markers significantly decreased after supplementation [26]. After 6 weeks of radiochemotherapy, 19 of the 31 eligible patients experienced at least an NCI grade 3 or 4 acute toxicity, including five patients (16%) with grade 3 or 4 mucositis. The clinical relevance of this study is limited by the lack of a control group. However, the authors highlight that in their study the incidence of severe acute mucositis was 16 vs. 45% in the available and comparable literature [26].

Although published studies are inconclusive due to the small populations involved and the lack of control groups, nevertheless the robustness of observational studies seems to suggest a causative inverse link between muscle mass and cancer treatment toxicity. Therefore, the role of muscle mass in preventing chemotherapy-induced toxicity should be further investigated, and factors associated to muscle mass, that is, physical exercise or drug pharmacokinetics, should also be considered.

Neutropenia and impaired neutrophil function are frequent toxic effects of cancer chemotherapy and lead to dose reduction when severe. Bonatto et al. [27] recently tested whether omega-3 fatty acids supplementation improved neutrophil function in cancer patients receiving chemotherapy. Results show that nonsupplemented cancer patients receiving 5-fluorouracil and leucovirin lost 2.5 kg of weight over the 8 weeks of the study. Also, the number of blood polymorphonuclear cells, mainly neutrophils, and their functions (phagocytosis and hydrogen peroxide production) significantly decreased. In contrast, daily supplementation of 0.3 g EPA and 0.4 g DHA prevented these decreases and actually increased body weight, polymorphonuclear cell number, phagocytosis and superoxide production. These results are encouraging but more trials are needed to assess whether the protective effects of EPA and DHA on neutrophil number and function translate into clinically relevant outcomes (i.e. prevention of infections, reduction of treatment interruptions due to neutropenia).

OMEGA-3 FATTY ACIDS AND RESPONSE TO TREATMENT

The tumour inflammatory microenvironment plays a major role in growth, invasiveness and resistance to therapy [28]. On the contrary, food is a potent inducer of metabolic responses. Therefore, modulation of food intake may impact on tumour growth, by sensitizing cancer cells to chemotherapy and increasing resistance of normal cells to the toxic effects. In animal models, this hypothesis has been tested by using extreme nutritional stress. Lee et al. [29] studied the effects of short term fasting on cultured cancer cells and in animal models. Results obtained showed that multiple cycles of fasting promote differential stress sensitization in a wide range of tumours and could potentially replace or augment the efficacy of certain chemotherapy drugs in the treatment of various cancers [29]. However, translation of this approach in clinical practice could be difficult and not advisable since cancer patients are already prone to the development of malnutrition and cycles of fasting may accelerate the onset of cachexia [30]. Since tumour growth appears to be related to the circulating levels of glucose and insulin-like growth factor I (IGF-I) [29], any nutritional intervention inhibiting the IGF-I axis may also lead to increased sensitization of cancer cells to chemotherapy and increased resistance of normal cells to cancer treatment toxicity. Interestingly, experimental evidence showed that
plasma IGF-I decreased with increasing dietary omega-3 : omega-6 ratio [31]. Therefore, omega-3 fatty acid supplementation could represent a clinically relevant adjuvant therapy in cancer patients.

Recent evidence shows that omega-3 fatty acid supplementation increases cancer cell apoptosis. Benais-Pont et al. [32] demonstrated that preincubation with omega-3 fatty acids induced a dose-dependent additive decrease in colorectal cancer cell survival after irradiation. Evaluation of the underlying mechanisms indicated that omega-3 fatty acids mainly decreased the cell number via apoptosis induction [32]. Supporting this evidence, Fukui et al. [33] demonstrated that feeding animals with a diet supplemented with high levels of EPA and DHA inhibits the growth of human pancreatic cancer xenografts in athymic nude mice by inducing oxidative stress and cell death. However, EPA can concomitantly induce autophagy in cancer cells, and the induction of autophagy diminishes its ability to induce apoptotic cell death [33].

In cancer patients, promising results have been obtained. Bougnoux et al. [34] evaluated the safety and efficacy of the addition of 1.8 g DHA daily to an anthracycline-based chemotherapy regimen in 25 breast cancer patients with rapidly progressing visceral metastases. Results obtained showed that the objective response rate, time to progression and overall survival were within the ranges reported in the literature [34]. However, when patients are stratified according to high or low DHA incorporation into cell membranes, survival is almost doubled in high incorporating vs. low incorporating patients (34 and 18 months, respectively) and longer than the average overall survival reported in the literature, that is, 18–23 months [34]. It is likely that tumour cells were made more sensitive to chemotherapy when membrane lipids were enriched with DHA, an oxidative stress-inducing lipid [34]. More recently, Murphy et al. [25**] studied 46 lung cancer patients receiving first-line chemotherapy. Patients were invited to take fish oil (2.5 g EPA + DHA/day) during chemotherapy cycles, as tablets or liquid product. At the end of the study, patients supplemented with fish oil \((n = 15)\) had an increased response rate (60.0 vs. 25.8%) and greater clinical benefit (80.0 vs. 41.9%) when compared to those observed in the standard of care group. Surprisingly, the incidence of dose-limiting toxicity did not differ between groups although fish oil supplementation increased their muscle mass [20,25**]. Also, 1-year survival tended to be greater in the fish oil group (60.0 vs. 38.7% \((P = 0.15)\) [25**].

When considered together, this evidence suggests that omega-3 fatty acids may exert a direct inhibitory effect on cancer cells \(\text{in vivo}\) (proapoptotic effect?), beyond their potential for reducing cancer treatment toxicity. Considering the cost of omega-3 fatty acid supplementation when compared to chemotherapy, even achieving a 30% increase in response rate by integrating EPA/DHA in standard treatment of cancer patients would prove to be highly cost-effective.

**CONCLUSION**

Integration of omega-3 fatty acid supplementation into the therapeutic approach to cancer patients is a novel and promising concept, which goes beyond their potential role in reversing cancer cachexia, promoting weight maintenance and improving muscle mass. Preliminary observations suggest that statistically significant and clinically relevant achievements could be obtained in terms of enhanced efficacy of anticancer drugs, reduced toxicity and enhanced quality of life. The next frontier is including nutrition therapy into clinical trials testing the efficacy of chemical entities in cancer patients: in this way, by testing this combination in a large population, a definitive answer to the therapeutic role of omega-3 fatty acids will be achieved and general recommendations could be issued. Evidence in this area is being constantly produced, which strongly suggests the general tenet of clinical nutrition, that is, ‘never underestimate the power of food’.

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**Conflicts of interest**

Alessandro Laviano has received honoraria and research funds from Abbott, Baxter, BBraun, Danone Research, Fresenius-Kabi, Nestlé Health Science.

Serena Riamonta: No conflict to disclose.

Alessio Molfino: No conflict to disclose.

Filippo Rossi Fanelli has received research funds from Fresenius Kabi.

**REFERENCES AND RECOMMENDED READING**

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).


Very good opinion paper advocating the need to reconsider current cancer care which is burdened by high costs and limited clinical benefits.

Lipid metabolism and therapy


Very good and updated review article, detailing the mechanisms responsible for the anti-inflammatory properties of omega-3 fatty acids.


Solid epidemiological study showing that consumption of omega-3 fatty acid-rich fish or omega-3 fatty acids, particularly EPA and DHA, appears to protect against the development of hematopoietic carcinoma, even among patients with HBV and/or HCV infection.


Very recent systematic review incorporating the most recent trials addressing the potential causal relationship between dietary omega-3 fatty acids and cancers and therefore expanding beyond the previous FAO/OMS expert consultation.


International consensus on the definition of cancer cachexia and on its diagnostic criteria. Of the utmost importance, this study proposes a strategy to cancer cachexia staging.


Important paper demonstrating that sarcoma predicts postoperative infections, inpatient rehabilitation care and consequently a longer LOS in colorectal cancer patients undergoing surgery.


This study shows that obesity and sarcopenic obesity are highly prevalent in cancer patients and that muscle depletion is associated with worse outcome irrespective of the BMI class.


Comprehensive systematic review on the impact of omega-3 fatty acids, either enterally supplemented or parenterally infused in different clinical settings. Results obtained show some benefit in cancer patients on weight maintenance and quality of life.


Systematic review assessing the impact of fish oil oral supplementation on cancer cachexia. Results show that there are insufficient data to draw definitive recommendations.


Important study, although limited by the small number of patients enrolled, which demonstrates that omega-3 fatty acid supplementation on top of energy and protein requirement results in improved body function even in cancer patients undergoing active treatment.


Interesting study showing that muscle depletion during active treatment is not inevitable since omega-3 fatty acid supplementation results in improved skeletal muscle mass.


This opinion paper authored by eminent oncologists recognizes that cancer treatment toxicity is an under-recognized clinical problem. However, the authors fail to recognize that maintenance/restoration of muscle mass is a promising therapeutic strategy to limit cancer treatment toxicity.


Clinical trial directly linking sarcopenia and toxicity associated with the use of novel ‘intelligent’ chemotherapeutic drug.


Although the methodology of the study is suboptimal due to the lack of randomization, the results are outstanding, since they report that fish oil supplementation doubles the response rate of lung cancer patients receiving first-line chemotherapy.


Good study showing that cancer chemotherapy-induced neutropenia could be prevented by long-term fish oil supplementation. Remains to be tested whether this effect translates into clinically relevant outcome measures.


Provocative study showing in different experimental conditions that short-term fasting triggers a differential response in cancer cell and normal cells, thereby circumventing sensitizing cancer cells and increasing resistance of normal cells to toxicity.
