The Role of Eicosapentaenoic Acid in the Treatment of Cancer Patients

a report by

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DOI: 10.17925/EOH.2006.0.2.110

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Cancer-induced Weight Loss

Wide alterations in carbohydrate, lipid and protein metabolism in the tumour-bearing host have been previously documented. Cancer anorexia/cachexia is characterised by a shift in nutrient use from the growth and maintenance of muscle mass to processes that support the immune response and affect disease resistance.[1] These changes can result in an increased rate of muscle protein degradation and increase in acute-phase protein synthesis, with progressive depletion of lean body mass, with clinical evidence of cachexia. The majority of cancer patients experience weight loss as their disease progresses and, in general, weight loss is a major prognostic indicator of poor survival and impaired response to anti-neoplastic therapy.

Cancer cachexia is a multifactorial event and inflammation plays a relevant pathogenetic role. Studies have demonstrated that a variety of pro-inflammatory cytokines can lead directly to development of anorexia and metabolic changes and can be associated with the development of cachexia. In addition, the presence of a pro-inflammatory response (documented by an acute phase protein response) has been associated in a variety of human malignancies with accelerated weight loss, anorexia, hypermetabolism and a shortened duration of survival.

Not surprisingly, conventional nutritional support, whether in the form of oral feeding, enteral feeding or parenteral nutrition, has generally failed to either prolong survival or improve the outcome of conventional anti-neoplastic therapy.

Fish Oil and Eicosapentaenoic Acid

In healthy individuals and in patients with cancer, the production of pro-inflammatory cytokines such as interleukin (IL) 6, IL-1 and tumour necrosis factor (TFN) can be downregulated by omega-3 poly-unsaturated fatty acid (FA) and eicosapentaenoic acid (EPA). Furthermore, the effects of proteolysis-inducing factor (PIF), a cachectic factor produced by cancer tissue, are also inhibited by EPA.

In 1996, Wigmore et al. evaluated the effects of EPA in 18 patients with cachexia due to unresectable pancreatic cancer.[2] The patients received approximately 12g of fish oil per day (2g of EPA per day) over a period of three months. This was associated with the arrest of cachexia in the majority of patients, with a small proportion of patients actually gaining weight. These findings contrast markedly with the natural history of pancreatic cancer in which patients progressively lose weight.

Barber et al. evaluated the effect of an oral nutritional supplement enriched with fish oil on weight loss in patients with advanced pancreatic cancer.[3] After administration of the fish oil-enriched supplement, patients had a significant weight gain at both three (median 1kg, $p=0.024$) and seven weeks (median 2kg, $p=0.033$). Resting energy expenditure per kg body weight and per kg lean body mass fell significantly. Performance status and appetite were significantly improved at three weeks.

The positive effects of EPA-rich nutritional supplements in the treatment of advanced pancreatic cancer with weight loss was subsequently confirmed by Fearon et al., with evidence of lean body mass increase and increased quality of life after treatment for two months.[4] These results were obtained with *post hoc* dose response analysis which showed that, in order to achieve a net gain of body weight and lean body mass, a daily consumption of 1.5–2 cans of supplement enriched with n-3 FAs and antioxidants was required for two months. This corresponds to 1.5–2g/day of EPA and to 450–600kcal/day. A similar intake of nutritional supplement enriched with EPA was associated with a significant increase of physical activity level (PAL) and of total energy expenditure (TEE), showing that patients with pancreatic cancer could almost reach a normal sedentary level of activity (Moses et al).[5] These positive results were not confirmed by some subsequent studies,[6] but this discrepancy could be explained by differences in the selection criteria of cancer patients and of the intervention protocol.

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* EPA = eicosapentaenoic acid, an omega-3 fatty acid derived from fish oil

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The parenteral administration of omega-3 FAs has also been evaluated. Parenteral treatment with an emulsion with reduced content of n-6 FAs, an increased share of monounsaturated FA and n-3 FA, and supplemental vitamin E is well tolerated and modulates FA and leukotriene patterns, suggesting favourable anti-inflammatory effects and further clinical benefits.[7]

New and interesting data are also available on the effects of fish oil on reduction of carcinogenesis and on reduction of the chemotherapy dose. Epidemiological studies have indicated that a high intake of saturated fat and/or animal fat increases the risk of colon and breast cancer. Laboratory and clinical investigations have shown a reduced risk of colon carcinogenesis after alimentation with omega-3 FA, as found in fish oil. Mechanisms accounting for the anti-tumour effects are reduced levels of prostaglandin E(2) and inducible nitric oxide synthase as well as an increased lipid peroxidation, or transplantation inhibition with subsequent cell cycle arrest.[8]

Additional interest in the field of cancer cachexia comes from the experience of Bossola et al. who showed hyper-expression of messenger RNA for ubiquitin and increased proteolithic activity of proteasome before weight loss in cancer patients.[9] This experience could open a new research area in the field of early intervention and of prevention of cancer-induced weight loss. Another problem that requires additional research is cancer anorexia, due to the frequent finding of reduced food intake in cancer patients and to the lack of powerful therapy to improve appetite and daily caloric intake.

Conclusions

Cancer-induced weight loss (cachexia) is a complex, multifactorial syndrome that results from a reduction in food intake or a variety of metabolic abnormalities (including hypermetabolism) or, more often, a combination of the two. Multiple mediator pathways including proinflammatory cytokines, neuro-endocrine hormones and tumour-specific factors are involved. Therapy requires a multimodal approach that addresses both reduced food intake and metabolic change. Combination treatment such as nutritional support plus metabolic/inflammation modulation with EPA promises improved functional capacity and quality of life. Further research is needed to identify the optimal therapeutic approach in the different clinical settings of patients with cancer-induced weight loss. In particular the early appearance of biological alterations associated with cachexia development suggests a potential role for early intervention, beside treatment of the advanced stages of cancer malnutrition. ■

Cancer cachexia is a multifactorial event and inflammation plays a relevant pathogenetic role.

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