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Current Controversies in Cancer

Should Cancer Patients with Incurable Disease Receive Parenteral or Enteral Nutritional Support?

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INTRODUCTION

PATIENTS WITH advanced cancer are frequently malnourished and, in some cases, this is the dominant symptom of their disease. For such patients, nutritional support seems not only logical, but also humane. However, in the anorectic or weight-losing cancer patient, an increase in spontaneous oral diet is often difficult to achieve and the more invasive techniques of enteral or parenteral feeding incur their own complications and restraints in a group already suffering impaired quality of life. Moreover, it is unclear whether, in cancer patients, the constituents of conventional nutritional support are effective in repleting fat and muscle stores. In spite of these problems, recent advances in our understanding of the mechanisms of weight loss in cancer and the physiology of certain nutrients means that there is considerable reason for optimism. Thus, the aim of this article is to support the proposal that nutritional intervention is, or soon will be, of value in those with incurable cancer.

Trials of nutritional intervention have traditionally focused on end-points such as nitrogen balance, immune status, weight and hospital stay. However, these are merely surrogate markers for the factors which are genuinely important to the patient, namely quality and quantity of life. Unfortunately, measurements of quality of life and survival have been used infrequently in trials of conventional nutritional supplementation. Moreover, whilst current research has concentrated on achieving more optimal repletion of lean tissue in wasted cancer patients, it must be remembered that a benefit in a surrogate marker does not necessarily equate to a true patient benefit (Figure 1) and that nutritional end-points and quality of life therefore need to be assessed simultaneously. The literature will be discussed in the light of these limitations.

EFFECT OF CONVENTIONAL APPETITE STIMULANTS AND NUTRITIONAL THERAPY IN ADVANCED CANCER

The provision of wholesome, appetising food in hospitals, patients' homes and hospices, together with control of anorexia-inducing symptoms (such as pain and nausea), is a necessary first step in allowing patients with advanced cancer to eat more normally. Eating a meal is a central component of normal social integration and, thus, this simple form of nutritional support has genuine benefits for individual patients in terms of their quality of life. Conventional end-points may not be altered dramatically and so the overall efficacy may be difficult to assess, but this does not diminish the importance of such intervention.

Appetite stimulants, such as synthetic progestogens and steroids, are a useful component of therapy when trying to get anorectic patients with advanced cancer to eat more normally. A recent controlled trial of medroxyprogesterone acetate in advanced, incurable cancer has shown an improvement in appetite and an attenuation of weight loss. However, there was no improvement in quality of life or survival compared with controls [1]. Similarly, prednisolone has been shown to improve appetite and may have a small effect on well-being. However, it does not increase food intake or affect weight in those with cancer [2] and its beneficial effects often persist for only a limited period of about 4–6 weeks. It would, therefore, appear that although appetite stimulants may treat anorexia, this frequently does not translate into improved nutritional status. The effects on quality of life are variable and may or may not be dependent on change in nutritional status. Further research on the control of appetite may allow more effective intervention in the future [3].

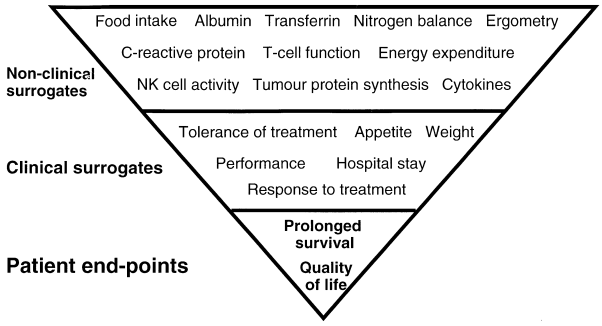

Figure 1. Targets for nutritional therapy in advanced cancer.

Nutritional supplements or sip feeds are a useful method of supplying calories and protein in a small volume to patients suffering from a reduced appetite or early satiety. Ovesen and colleagues studied 105 patients receiving chemotherapy randomised to receive nutritional counselling advocating such supplements or not [4]. Nutritional counselling increased food intake but had no significant effect on nutritional status, response rate, survival or quality of life over 5 months. A similar study in 192 patients receiving chemotherapy with randomisation to nutritional counselling also succeeded in raising calorie intake but once again there was only a limited effect on nutritional parameters over 12 weeks and no effect on response to chemotherapy or survival [5]. These trials suggest that a relatively small improvement in nutritional intake alone may not be enough to alter the nutritional status or function of patients with advanced cancer.

Studies of enteral tube feeding and total parenteral nutrition (TPN) in cancer are necessarily performed over relatively short periods of time and this tends to limit the improvements in body composition that may be achieved. Enteral tube feeding may result in a gain in body weight, but body composition analysis reveals that this is mainly due to gains in body water and fat rather than lean tissue [6] and studies of quality of life and other parameters are lacking. Similar findings have been described in relation to TPN [6, 7], again emphasising the suboptimal response to conventional nutritional support in cancer. In 1989, the American College of Physicians concluded that, due to increased complications, parenteral nutrition in patients with advanced cancer was associated with net harm and that in broad terms no patient group could be defined in which such therapy was of benefit [8]. Nevertheless, cancer is a frequent indication for home parenteral nutrition in Europe [9]. However, these patients represent only a small fraction of the total cancer patient population and whilst there is no doubt that clinicians will occasionally see patients with good potential for meaningful prolonged survival for whom home TPN appears to be of benefit, it seems unlikely that it will be possible to convert these anecdotal reports to positive findings in a trial.

FUTURE DEVELOPMENTS TO ACHIEVE EFFECTIVE NUTRITIONAL THERAPY

It is now clear that at least a proportion of cancer patients have widespread alterations in substrate metabolism associated with abnormal endocrine hormone and cytokine profiles [10–13]. These factors create a condition similar to the so-called 'metabolic response to trauma', resulting in reduced caloric intake, increased energy expenditure, inefficient use of nutrients and a pro-inflammatory state with net protein breakdown. This acute phase response may be beneficial in situations such as trauma or infection (by providing substrates to aid the defence of the body), but in a chronic condition, such as cancer, it may lead to accelerated weight loss and resistance to nutritional intervention. Recently there has been interest in specific components of the diet and their potential to modulate the metabolic response to injury. New terms have emerged such as 'functional foods', 'immunonutrition' or 'nutraceuticals'. Interest has focused on the amino acids arginine and glutamine, essential fatty acids (particularly eicosapentaenoic acid), nucleotides and combinations of these nutrients. The relevance of these substrates to the weight-losing cancer patient is discussed below.

Arginine

Arginine is not considered an essential amino acid but, like glutamine, may become at least semi-essential in conditions of stress, sepsis and trauma. It is a substrate for protein, creatinine, polyamine and nitric oxide synthesis. Its beneficial effects as a nutrient may be through modulation of the immune system [14, 15].

In a controlled trial of enteral nutrition supplemented with 25 g arginine per day in cancer patients for 7 days after major surgery, Daly and coworkers found that nitrogen balance returned more quickly with arginine [16]. They also observed an enhanced T-lymphocyte response and increased percentage of lymphocytes expressing helper phenotype in patients receiving arginine. However, there were no differences in clinical outcome and quality of life was not assessed.

Thirty grams of arginine per day for 3 days prior to chemotherapy for breast cancer resulted in a response rate better than that of historical controls [17], and arginine added to a complex mixture of other immunomodulatory nutrients (including n-3 fatty acids) has been associated with fewer complications and a shorter hospital stay in a randomised trial of patients undergoing major surgery for upper gastrointestinal cancer [18].

Taken together these findings suggest nutritional support with extra arginine may be beneficial for the potentially curable patient undergoing concomitant chemotherapy or surgery. Whether this would translate into benefit for patients with incurable cancer remains to be addressed.

Glutamine

Glutamine is the most abundant amino acid in the body and, although it is not usually essential, it may become so in conditions of stress. It has important roles in nitrogen transport, in nucleotide and protein synthesis and as a fuel for the gut mucosa, the kidney and lymphocytes. Its potential beneficial action in those with advanced cancer may be principally through modulation of the gut and systemic immune systems [19]. Glutamine slowly degrades into pyroglutamic acid and, therefore, despite its potential importance, it is usually excluded from conventional TPN.

Supplementation of TPN with 0.57 g/kg/day glutamine for 28 days after bone marrow transplantation for haematological malignancy resulted in improved nitrogen balance, reduced incidence of infection and shorter hospital stay compared with controls [20]. A further study in a similar group of patients confirmed a significantly reduced hospital stay, but found no differences in complications [21]. Although long-term survival was not assessed in either study, these results suggest a benefit in outcome and quality of life when conventional

TPN is supplemented with glutamine for specific groups of patients with cancer.

n-3 Fatty acids

Polyunsaturated fatty acids of the n-3 class, such as eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) cannot be synthesised by mammals, but are required for the maintenance of health. They have numerous roles determining cell membrane fluidity, receptor, enzyme and second messenger function, and in eicosanoid synthesis.

Supplementation with approximately 2 g/day of n-3 fatty acids in a mixed fish oil preparation in healthy volunteers, down-regulates production of the pro-inflammatory cytokines interleukin (IL)-1β, tumour necrosis factor and IL-6 by peripheral blood mononuclear cells and leads to a reduced T-lymphocyte mitogen response [22]. In the advanced cancer patient, these effects could be detrimental if cytokines and T-lymphocytes were required for tumour immunosurveillance. However, pro-inflammatory cytokines also induce the acute-phase protein response and are implicated in cachexia and a poor prognosis in advanced cancer [11]. A reduction in pro-inflammatory cytokine activity following EPA administration might therefore be of benefit. EPA also appears to inhibit novel proteolytic and lipid-mobilising factors associated with the development of cachexia in an animal model [23].

In a study of fish oil rich in n-3 fatty acids at a dose of 2 g EPA/day in patients with advanced pancreatic cancer, we showed a significant attenuation of cachexia [24]. A further study confirmed this effect in a trial of 6 g/day of high purity EPA in a similar group of patients who went from losing a median of 2 kg/month before administration of EPA to a median weight gain of 0.75 kg after 1 month with weight stability thereafter [25]. Survival in this uncontrolled study was better than in untreated historical patients.

n-3 fatty acids would seem to normalise some of the underlying metabolic abnormalities in cachectic patients with advanced cancer and might, therefore, allow a better response to nutritional support.

CONCLUSION

The anecdotal but important benefits of paying attention to the promotion of simple oral nutrition in patients with advanced cancer should not be forgotten. However, there seems little doubt that aggressive *conventional* nutritional support in the form of tube enteral supplementation and parenteral nutrition has limited benefits for the majority of cancer patients, perhaps due to the underlying metabolic changes seen in cancer. Although some of these abnormalities may be overcome by specific nutrients, it is important that as studies of these agents move into the clinical arena, close attention is paid to the conduct of such trials. Well defined end-points and careful measures of nutritional status, quality of life and survival are required. The tools available for the study of nutrition-related quality of life issues are at present somewhat blunt. None the less, their use is vital to progress in the field. Expecting miracles is not appropriate but investigation of the benefits of specific forms of nutritional intervention in specific situations may bring substantial benefits for our patients.

1. Simons JPFHA, Aaronson NK, Vansteenkiste JF, *et al.* Effects of medroxyprogesterone acetate on appetite, weight, and quality of life in advanced-stage non-hormone-sensitive cancer: a placebo-controlled multicenter study. *J Clin Oncol* 1996, **14**, 1077–1084.
2. Willox JC, Corr J, Shaw J, Richardson M, Calman KC, Drennan M. Prednisolone as an appetite stimulant in patients with cancer. *Br Med J* 1984, **288**, 27.
3. Schwartz MW, Seeley RJ. Neuroendocrine responses to starvation and weight loss. *N Engl J Med* 1997, **336**, 1802–1811.
4. Oveson L, Allingstrup L, Hannibal J, Mortensen EL, Hansen OP. Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomised study. *J Clin Oncol* 1993, **11**, 2043–2049.
5. Evans WK, Nixon DW, Daly JM, *et al.* A randomised trial of oral nutritional support versus *ad lib* nutritional intake during chemotherapy for advanced colorectal and non-small-cell lung cancer. *J Clin Oncol* 1987, **5**, 113–124.
6. Cohn SH, Vartsky D, Vaswani AN, *et al.* Changes in body composition of cancer patients following combined nutritional support. *Nutr Cancer* 1982, **4**, 107–119.
7. Nixon DW, Lawson DH, Kutner M, *et al.* Hyperalimentation of the cancer patient with protein-calorie undernutrition. *Cancer Res* 1981, **41**, 2038–2045.
8. American College of Physicians. Parenteral nutrition in patients receiving cancer chemotherapy. *Ann Intern Med* 1989, **110**, 734–736.
9. Gossum A van, Bakker H, Francesco A de, *et al.* Home parenteral nutrition in adults: a multicentre survey in Europe in 1993. *Clin Nutr* 1996, **15**, 53–59.
10. Fearon KCH, Hansell DT, Preston P, *et al.* Influence of whole body protein turnover rate on resting energy expenditure in patients with cancer. *Cancer Res* 1988, **48**, 2590–2595.
11. Falconer JS, Fearon KCH, Plester CE, Ross JA, Carter DC. Cytokines, the acute-phase response, and resting energy expenditure in cachectic patients with pancreatic cancer. *Ann Surg* 1994, **219**, 325–331.
12. Todorov P, Cariuk P, McDevitt T, Coles B, Fearon K, Tisdale M. Characterisation of a cancer cachectic factor. *Nature* 1996, **379**, 739–742.
13. Wigmore SJ, Plester CE, Ross JA, Fearon KCH. Contribution of anorexia and hypermetabolism to weight loss in anicteric patients with pancreatic cancer. *Br J Surg* 1997, **84**, 196–197.
14. Brittenden J, Heys SD, Ross J, Park KGM, Eremin O. Natural cytotoxicity in breast cancer patients receiving neoadjuvant chemotherapy: effects of L-arginine supplementation. *Eur J Surg Oncol* 1994, **20**, 467–472.
15. Brittenden J, Park KGM, Heys SD, *et al.* L-arginine stimulates host defenses in patients with breast cancer. *Surgery* 1994, **115**, 205–212.
16. Daly JM, Reynolds J, Thom A, *et al.* Immune and metabolic effects of arginine in the surgical patient. *Ann Surg* 1988, **208**, 512–521.
17. Brittenden J, Heys SD, Miller I, *et al.* Dietary supplementation with L-arginine in patients with breast cancer (> 4 cm) receiving multimodality treatment: report of a feasibility study. *Br J Cancer* 1994, **69**, 918–921.
18. Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. *Ann Surg* 1995, **221**, 327–338.
19. O'Riordain MG, Fearon KCH, Ross JA, *et al.* Glutamine-supplemented total parenteral nutrition enhances T-lymphocyte responses in surgical patients undergoing colorectal resection. *Ann Surg* 1994, **220**, 212–221.
20. Zeigler TR, Young LS, Benfell K, *et al.* Clinical and metabolic efficacy of glutamine-supplemented parenteral nutrition after bone marrow transplantation. A randomised, double-blind, controlled study. *Ann Intern Med* 1992, **116**, 821–828.
21. Schloerb PR, Amare M. Total parenteral nutrition with glutamine in bone marrow transplantation and other clinical applications (a randomised, double-blind study). *JPEN J Parenter Enteral Nutr* 1993, **17**, 407–413.
22. Meydani SN, Endres S, Woods MM, *et al.* Oral (n-3) fatty acid supplementation suppresses cytokine production and lymphocyte proliferation: comparison between young and older women. *J Nutr* 1991, **121**, 547–555.
23. Tisdale MJ. Inhibition of lipolysis and muscle protein degradation by EPA in cancer cachexia. *Nutrition* 1996, **12**(Suppl. 1), S31–S33.

24. Wigmore SJ, Ross, JA, Falconer JS, *et al.* The effect of polyunsaturated fatty acids on the progress of cachexia in patients with pancreatic cancer. *Nutrition* 1996, **12**(Suppl. 1), S27–S30.

25. Barber MD, Wigmore SJ, Ross, JA, Fearon KCH. Eicosapentaenoic acid attenuates cachexia association with advanced pancreatic cancer. *Prostaglandins Leukot Essent Fatty Acids* (in press).

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NUTRITIONAL SUPPORT in cancer patients should show a beneficial impact on survival, disease-free survival, response to antineoplastic therapy, toxicity, nutritional status or quality of life. Additionally, nutritional interventions should not enhance tumour growth while repleting lean body mass and fat stores. There is (conflicting) evidence that intravenous hyperalimentation may stimulate tumour growth and mitotic activity in animals, while caloric restriction results in inhibition of tumour growth [1]. Tumour growth in response to starvation and refeeding is rapid and reproducible [2], a process in which sugars seem to have the most pronounced stimulating effect. So far, these effects have been shown in an animal model; hyperalimentation does not seem to promote tumour growth in humans [3]. A large study demonstrated that maintenance of a good nutritional status in patients with malignant lymphoma does not have any deleterious effect on tumour growth [4]. Such research is relevant, since some more recent nutritional concepts are based on the assumption that the tumour and the tumour-bearing host have a different energy substrate utilisation [5]. Today, the following facts are accepted concerning nutrition-related tumour growth: starvation is more harmful to the tumour-bearing human than to the tumour itself; energy substrate composition may have an impact on tumour growth (low carbohydrate content, high fat content); the role of glutamine, arginine, fatty acids and polyribonucleotides is becoming evident [6–12].

The prevalence of nutritional deficits in cancer patients is high; cachexia has a dramatically negative influence on patient outcome. Besides the well-known immunological abnormalities with impaired tolerance of antineoplastic therapy leading to an increased morbidity and mortality, low quality of life is the main concern for the patient. Nutritional support in this situation would, of course, make good sense, but until now, scientific data have not been convincing evidence that nutritional interventions, at least in the conventional way, are really beneficial to the patient with incurable malignancy. Nutritional therapy alone or in conjunction with antineoplastic therapy (surgery, radiotherapy, chemotherapy, immunotherapy) has failed to become an accepted supportive modality, and there is no consensus regarding its therapeutic role so far.

The reasons for this dilemma are found in inappropriately designed nutritional intervention trials and nutrition-related inefficiencies [13–19]. However, subsequent randomised studies have been unable to demonstrate a clear positive effect on tumour response, toxicity or survival [20, 21]. In more recent studies with improved methodology (and better energy substrates), no other conclusions can be drawn [22]: more than 70 prospective randomised controlled trials have evaluated the use of nutritional support in cancer patients, but many trials had serious shortcomings in study design that limited the ability to draw definitive conclusions from the data. In general, the data failed to demonstrate the clinical efficacy of providing nutritional support to most patients with cancer. Nutritional effects may be limited, due to the usually short duration of nutritional support, while malnutrition in cancer patients occurs over several months [23]. Unfortunately, quality of life issues have usually not been considered important endpoints [24]. In special settings, such as chronic gastrointestinal insufficiency (short bowel, radiation enteritis) or prolonged intestinal toxicity (bone marrow transplantation as an example), nutritional support has an established role; in the settings mentioned the patient is either cured (nutritional rehabilitation) or treated with curative intent [25, 26].

Peri-operative nutritional support is still under debate; preoperative total parenteral nutrition (TPN) is able to reduce postoperative morbidity and mortality [27]. Pooled data from 18 controlled clinical trials of peri-operative TPN demonstrated that only certain subgroups of patients who are at a particularly high risk would have benefitted [28]. It still remains unclear, again due to inadequate sample sizes and suboptimal nutritional support, which patient may benefit from peri-operative nutritional therapy. A randomised trial of postoperative TPN after pancreatic surgery for malignancy demonstrated a detrimental effect (infectious complications) [29]. Multicentre randomised trials with relevant endpoints, including quality of life, are warranted. It must be noted that conventional parenteral or enteral nutritional support may influence postoperative outcome positively (hence also justifying the procedure in patients with advanced incurable cancer), but most probably not the general outcome of malignant disease.

Nutritional support as an adjunct to radiotherapy may have a role concerning tolerability. Radiation therapy, depending on dose and location, can influence nutritional status considerably; patients with head and neck cancer demonstrate a high risk for intestinal toxicity, often precluding normal enteral intake. Concomitant nutritional support,

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