Nutritional interventions improve QoL

Jens Kondrup, MD, PhD
Copenhagen, Denmark

Around 35% of cancer patients have already experienced weight loss by the time of diagnosis. With the steady increase in the number of patients being diagnosed with cancer the problem of malnutrition in these patients will also increase.

Can nutritional intervention improve the quality of life in these patients? Since 1982 there have been 18 RCTs which have investigated the contribution of nutritional support to QoL. Early studies were characterised by the use of custom-made and non-standardised QoL scales, and in these studies there appeared to be little benefit of nutritional intervention. However, within the last 10 years, evaluation tools have become more standardised, with the EORTC scale and the SF-36 figuring prominently in later studies. When these scales are used, results are more positive, showing an improvement in patient QoL with nutritional intervention. In these later studies, investigators selected QoL tools that are sensitive to nutritional support and also selected patients that are more likely to respond positively.

Baldwin et al (2012) published a meta-analysis of trials investigating oral nutritional supplements (ONS) in malnourished patients with cancer and confirmed that ONS are effective at increasing nutritional intake and improving some aspects of quality of life (QoL). Overall, 11 of the 17 studies demonstrated a positive effect. However a systematic review and cost-effectiveness calculations to be made to assess whether the intervention is desirable to the cost of treatment, assessed in terms of the price that a person is willing to pay to gain QALYs (quality adjusted life years).

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Utility derived from SF-36: SF-6D

<table>
<thead>
<tr>
<th>Physical functioning</th>
<th>Role physical</th>
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<tr>
<td>Role emotional</td>
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<td>Bodily pain</td>
<td>General health</td>
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<tr>
<td>Mental health</td>
<td>Vitality</td>
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1) Number of “dimensions” reduced by factor analysis
2) Each dimension given 2-6 well-defined levels (2.5^6 = 244)
3) Preference among 250 different health states evaluated by about 800 healthy volunteers
4) Each volunteer chose and ranked only 6 of the 250 health states (Good health + Almost dead)
5) Expressed as a value between 1 and 0.

Applying these measures to the patients in their 2008 intervention study, Norman et al (2011) were able to assess the cost of post-hospital supplementation with ONS relative to the improvement in QoL. In this study patients with benign GI disease and disease-related malnutrition were randomised on discharge from hospital to nutritional supplementation or to a control group that received dietary counselling. Patients were followed for 3 months with QoL being assessed using the SF-36 scale. The responses to this scale can be transferred to the SF-6D tool.

At baseline the two groups were equivalent in terms of health status. At 3 months, the health status utilities had increased significantly in the supplemented group. The nutritional intervention was associated with significantly higher costs, of 12,099 euros per QALY. However, international thresholds require that new treatments should improve QoL for no more 50,000 euros per QALY, so an annual cost of 12,099 euros is well within this limit. In the UK, technologies that cost between £20 and £30,000 per QALY are usually accepted.

To summarise, quality of life measures may be sensitive to nutritional supplementation in patients where hard end points such as death or complications are not. Measurements of QoL allow cost utility calculations to be made to assess whether the intervention is desirable and cost-effective.

Nutrition as part of treatment during neoadjuvant therapy

Christophe Mariette, MD, PhD
Lille, France

Survival in upper GI cancers is improved with a multimodal approach involving surgery, chemo- and radiotherapy rather than surgery alone. Nutrition is also an important factor, with 80% of patients already experiencing some degree of weight loss by the time of their diagnosis. The local effects of the tumour and...
the side effects of treatment can lead to reduced food intake: surgery can alter chewing and digestion, chemotherapy is often associated with nausea and vomiting, while radiotherapy can result in dysphagia, mucositis, taste alterations and difficulties in swallowing.

Malnutrition is a risk factor for post-operative complications in upper GI patients with a 10% decrease in body weight being predictive of post-operative complications.7-9 To improve the efficacy of treatments, approaches are needed to reduce chemo- and radiotherapy-related toxicities.10

There is evidence to support the benefits of enteral nutrition (EN) in cancer patients in the palliative and the peri-operative settings but in the neoadjuvant phase there is as yet less evidence to support its use.11-14 What we do know is that EN can prevent weight loss and promote adherence to treatment.

A 1994 review of seven randomised trials on nutritional support (EN) in the GI patient, mainly in the palliative setting, found no benefit in terms of survival, tumour response or chemotherapy-related toxicities.15 However, the studies included in this review were old, with small sample sizes and significant inequalities in terms of formula composition and the timing and duration of EN. A number of new studies have been published since then that offer a different view.

Hasenberg et al, reporting in 2010, found that parenteral nutrition (PN) during neoadjuvant chemotherapy in patients with metastatic colon cancer slowed weight loss, stabilised body composition, improved QoL and reduced chemotherapy-related toxicities.16 In 2012, Miyata et al compared the effects of EN and PN during neoadjuvant chemotherapy in randomised oesophageal cancer patients17 and found little difference regarding intake, serum albumin or body weight change, but found that EN reduced chemotherapy-related haematological toxicity (Figure 2). Finally, Lightart-Melis et al (2012) reported on the beneficial effects of intensive nutritional support (INS) during neoadjuvant chemotherapy for oesophageal cancer as a means of preserving pre-operative body weight and reducing severe post-operative complications.18

role of nutrition during neoadjuvant chemo

• Randomised trial – Results
  – Total and dietary intakes equal
  – Serum albumin or body weight change (ns)
  – Tumor response to chemo (EN 51%, PN 55%, ns)
  – Leukopenia grade 3 17% vs 41%, p=0.011
  – Neutropenia grade 3 36% vs 66%, p=0.005
  – Lymphopenia, thrombocytopenia, trend

  ➔ EN ▶ chemo-related hematological toxicity in OC

Miyata H Clin Nutr 2012

Figure 2: Role of nutrition during neoadjuvant chemotherapy

This new data has enabled the development of recommendations for the role of EN in oesophageal and gastric cancer patients receiving neoadjuvant therapy. In well-nourished patients, with a weight loss of less than 10%, patients should receive oral supplementation for a minimum of eight weeks until one week before surgery. During the final week they should receive for example oral Impact®, an immunonutrition supplement containing arginine, fish oil and nucleotides. Gastric cancer patients should undergo a jejunostomy to prevent severe post-operative weight loss.

Malnourished oesophageal cancer patients will benefit from placement of a tube for feeding before the start of neoadjuvant therapy while gastric cancer patients will benefit from a jejunostomy. Both types of patient will benefit from tube feeding during the neoadjuvant therapy phase until one week before surgery. Enteral Impact® (with the same constituents as above) should be given during this week and for one week after surgery, when oesophageal cancer patients will also receive a jejunostomy, and tube feeding will commence thereafter according to the status of the patient.10

A major trial, funded by Nestlé Health Science, is now under way to assess the impact of immunonutrition containing arginine, ω-3 fatty acids and nucleotides on the QoL of patients with non-metastatic upper GI cancer undergoing neoadjuvant treatment prior to surgery. This international phase III double-blind RCT which plans to recruit 356 patients, will test the hypothesis that immunonutrition given in this setting can improve tolerance to anti-neoplastic therapy, improve overall outcomes and improve QoL during and after all treatments.

In summary, malnutrition increases the risk for post-operative complications in patients with upper GI cancer and increases the toxicity of chemotherapy while reducing treatment responsiveness and QoL. A major trial has been set up to explore the role of nutritional support during treatment.

Specialised nutritional intervention during chemotherapy

Alessandro Laviano, MD
Rome, Italy

Over the last 20 years, despite an enormous amount of expenditure on research, overall and progression-free survival in advanced cancer is still limited. As treatments for cancer are very costly, researchers are increasingly focusing on strategies that will enhance the effectiveness of existing cancer treatments. There is evidence that nutritional support can have a beneficial effect on patient outcomes, improving nutritional status and immune response. Evidence is also emerging that specific nutritional components may help to reduce tumour growth.

It has been known for a long time that food is a potent inducer of metabolic responses. There are numerous examples of animals changing their diet in the short term in order to prevent or treat disease. With regards to cancer it is now known that tumour cells are able to adjust their inflammatory microenvironment to reduce and evade the host immune response, enabling them to proliferate and disseminate. There is a strong relationship between tumour cells and stromal cells, with the tumour cells adjusting their microenvironment through multiple interactions with the stromal cells to render them resistant to certain drugs.19

Also key is an inflammation-induced reduction in the host immune surveillance. In an experimental model of cancer cachexia it was possible to observe a strong decline in cell-mediated immunity even before body weight began to decline. It seems that the tumour may use inflammation as a way of reducing the immune response and to proliferate.20 This could serve as an early marker of cancer cachexia enabling supportive strategies to be put in place.

This is supported by a number of studies which demonstrate that it is possible to predict the aggressiveness of a tumour by the number of inflammatory cells infiltrating the stroma. This has been shown in for example breast cancer,21 invasive ductal carcinoma, non-small cell lung cancer, oesophageal carcinoma and malignant pleural mesothelioma (Figure 3).22
Invasive infiltrative lymphocytes in colorectal cancer patients. Samples of the impact of pre-operative immunonutrition and other diets on tumour modify tumour response. A recently published pilot study investigated studies investigating the potential for nutritional supplementation to receiving arginine supplementation, even after 10 years. Survival and overall survival were also significantly improved in patients receiving arginine supplementation, even after 10 years. Despite the controversial findings of this study, there are now numerous studies investigating the potential for nutritional supplementation to modify tumour response. A recently published pilot study investigated the impact of preoperative immunonutrition and other diets on tumour infiltrative lymphocytes in colorectal cancer patients. Samples of tumour were taken by endoscopy from four groups of patients receiving standard enteral diet, immunonutrition, normal nutrition or total parenteral nutrition for 7 days before surgery. Levels of CD4(+) , CD8(+) , CD16(+) and CD56(+) antibodies infiltrating the mucosal parts of the resected tumour tissue were evaluated. There was a significant increase in lymphocytes within the tumour tissue in the immunonutrition group, demonstrating that the inflammatory environment of the tumour can be changed with specific nutrients.

Another interesting area of study is the metabolism of fatty acids by the cytochrome P450 pathway leading to epoxy metabolites. These metabolites have a short half-life, but the quantity can be increased if the degrading enzyme is blocked. Epoxy metabolites of DNA are very potent tumour agents and have been shown to inhibit angiogenesis, tumour growth and metastasis in mice. Another aspect of nutrition and disease is the well-established practice amongst some oncologists of fasting patients before and during treatment. The rationale for this practice arose from a 2009 study which demonstrated a survival benefit on age-associated disease in animals of restricting calorie intake. However, a later study, using the same protocol found no benefit of caloric restriction on health and survival. The authors speculate that husbandry and the nature of the control diet may have been more important than caloric restriction. Today, it is acceptable to use starvation in certain patients but it is important at the same time to use the correct nutrients in the restricted diet. Short-term fasting does appear to activate a protective response in normal cells and to enhance the cytotoxic effect of chemotherapy. With the use of specific nutrients, it may be possible to prime the normal cell to be more resistant to the negative effects of chemotherapy, thereby achieving a reduction in side effects.

A ketogenic diet has been shown to be an effective adjuvant to radiation in reducing the spread of malignant glioma. Animals inoculated with this tumour were maintained on a standard or a ketogenic diet and received whole brain radiation followed by in vivo imaging. In 9 of 11 animals maintained on the ketogenic diet, the bioluminescent signal from the tumour cells diminished below the level of detection. The ketogenic diet appeared to enhance the anti-tumour effect of radiation.

To conclude, despite the investment of huge research resources, the efficacy of many cancer treatments is sub-optimal. Nutrition is not only a source of energy but is also a source of nutrients that may be able to re-programme gene expression. It has been shown that nutrition therapy can be very effective in cancer patients. Nutritional supplementation can treat cachexia which limits the effect of chemotherapy treatment. It may also exert direct anti-cancer activity although this needs to be investigated in large-scale trials.

**Nutrition modulation of chemotherapy toxicity**

![Vickie Baracos, PhD](image)

**Vickie Baracos, PhD**

Edmonton, Canada

Chemotherapeutic agents are designed to kill tumour cells and treatment at MTD (maximum tolerated dose) is usually required for efficacy. However, the therapeutic index of these agents is generally narrow, meaning that efficacy is also associated with significant toxicity. The oncologist has to strike a delicate balance between the efficacy and toxicity of chemotherapy for cancer.

There are two broad classes of antineoplastic agent, cytotoxic and targeted therapies, which have different biological mechanisms. Agents from the two classes are often combined in an attempt to improve efficacy without also increasing side effects. Cytotoxic agents tend to be fairly blunt and act on rapidly dividing cancer and normal cells by interfering with DNA replication and mitosis. Targeted therapies act with receptors on, or signal transduction within tumour cells, attacking signalling pathways and reducing cell proliferation.

An example of the impact of side effects can be seen with irinotecan, a DNA topoisomerase inhibitor. The major side effect is diarrhoea which emerges about 24 hours after treatment. This diarrhoea is usually unresponsive to loperamide, severe in 30 to 40% of patients and is life-threatening in around 8%. Aside from the discomfort and unpleasantness of side effects, a major problem is that they may lead to a dose reduction, a delay, or an interruption of treatment, all of which limit the benefits of chemotherapy.

The treatment planning process aims to find the optimum treatment for each patient taking into account efficacy, potential for toxicity and the renal and hepatic function of the patient. Nutritional status rarely plays a part in this decision-making despite the fact that nutritional status can be used to predict the toxicity of chemotherapy.

Cancer-associated depletion of body protein and energy reserves has been demonstrated using computer tomography (CT). In a recent paper, Prado et al (2013) demonstrated that progressive loss of adipose tissue and skeletal muscle in any tumour type, and for patients of any gender or age is strongly predictive of the risk of death (Figure 4). Chemotherapy itself contributes to further reductions in fat-free mass and in the incidence of severe muscle depletion (sarcopenia). Awd et al (2011) monitored a group of patients undergoing neoadjuvant chemotherapy for oesophago-gastric cancer. Patients had CT scans before and after treatment to derive estimates of fat-free mass and fat mass. During a period of 107 days, the proportion of patients with sarcopenia had increased from 57% to 79% along with reductions in fat-free mass and fat mass. In all, patients lost about 4.2 kg body weight. Patients with sarcopenia have a higher incidence of chemotherapy-related toxicity and decreased survival.

**Figure 3. Neutralizing Tumor-Promoting Chronic Inflammation: A Magic Bullet?**

This leads to the obvious question as to whether it is possible to use nutrition to neutralise the tumour inflammatory microenvironment or to boost host immune surveillance? A 2010 study in malnourished head and neck cancer patients showed that perioperative arginine-supplemented enteral nutrition improved long-term survival compared to those receiving a standard formula. Local recurrence-free survival and overall survival were also significantly improved in patients receiving arginine supplementation, even after 10 years.
Loss of muscle and fat over time to death in patients with solid tumors: analysis of n=1299 images

Figure 4. Association of muscle and fat with time to death

The impact of treatment on body mass is significant. In a typical patient undergoing surgery, reconstructive surgery and chemoradiation for head and neck cancer, around 7 kg body weight can be lost post-operatively, 4 kg of which is muscle, while a further 3 kg, half of which is skeletal muscle can be lost during subsequent chemoradiation. In as yet unpublished observations we have estab-lished that sarcopenia and weight loss in the six months prior to treatment are both independent predictors of treatment toxicity which may cause the patient to limit or interrupt treatment.

One mechanism for unwanted muscle wasting is that cancer therapeutic targets are also the pathways by which protein is synthesised: the TOR (target of rapamycin) pathway, for example, regulates cell growth, cell cycle progression and protein synthesis in skeletal muscle.32

Numerous published studies confirm that sarcopenia predicts toxicity in cancer patients. In patients with anthracycline-resistant metastatic breast cancer, 50% of sarcopenic patients experienced dose limiting toxicity during chemotherapy, compared to only 20% of nonsarcopenic patients (p<0.03).33 Time to tumour progression was also shorter in sarco- penic patients.

There is a vicious cycle of malnutrition and chemotherapy-related toxicity: toxicity aggravates the loss of muscle and fat tissue, while weight loss and sarcopenia enhance toxicity. The ideal way to break out of this cycle is to integrate weight loss and sarcopenia in cancer treatment planning. Nutritional assessment should be carried out at the earliest possible opportunity to allow better decision making. Treatment should be supported throughout by nutritional therapy if needed to enhance the efficacy of treatment and reduce toxicity.

The question of whether nutrition can help to reduce the toxicity of chemotherapy while improving efficacy has not been thoroughly studied. Bougnoux et al (2009) carried out a study in metastatic breast cancer patients to assess the impact of adding docosahexaenoic acid (DHA) to a FEC 75 chemotherapy regimen.35 Plasma phospholipid DHA levels were used to separate patients into poor and good incorporators of DHA. Overall survival of the two groups diverged significantly by 8 months, with mean time to tumour progression and overall survival significantly better in the DHA incorporators. The authors concluded that addition of DHA might improve the outcome of metastatic breast cancer patients but it is also possible that in this study the poor incorporators of DHA were further advanced in their disease. A new study, powered to detect survival as the primary endpoint, with results expected in 2014, should resolve this question (clinicaltrials.gov identifier NCT0148534).

In conclusion, better integration of oncology and nutrition with nutritional assessment incorporated into the treatment planning stage is needed along with validated algorithms incorporating the predictive power of nutritional status on survival. Studies are already required to assess the ability of nutritional supplements to enhance efficacy and reduce toxicity of chemotherapeutic agents.

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