Learning Objectives

- Understanding the impact of anti-cancer therapies on nutritional status;
- Understanding the negative role of caloric restriction/fasting on cancer patients’ nutritional status and outcome;
- Discussing the inhibitory role of specific nutrients on tumour growth;
- Discussing the role of specific nutrients in enhancing efficacy of anti-cancer therapies.

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Key Messages

- By altering taste and smell, chemotherapy reduces food intake;
- Specific chemotherapeutic agents have a negative and direct impact on muscle mass;
- Caloric restriction in vulnerable individuals, like cancer patients receiving active anti-cancer therapies, may favour weight loss and cachexia;
- Omega-3 fatty acids have been shown to enhance the efficacy of chemotherapy; although these preliminary results need to be validated in larger trials.
1. Introduction

Despite decades of scientific and financial efforts, cancer remains a leading cause of morbidity and mortality worldwide. During the recent past, the incidence of many human cancers progressively declined and the relative risk of cancer death in the first year after diagnosis also improved (1). Nevertheless, these results appear to be largely due to the worldwide implementation of prevention programmes and early screening procedures which allow timely eradicative therapies. In patients with advanced cancer, overall survival and progression-free survival are still limited, since the response rate to chemo- and radiotherapy is frequently below 50%. As an example, no more than 30% of patients with metastatic lung cancer benefit from first-line chemotherapy (2). Consequently, there is emerging awareness among oncologists that the current pharmacologic approach to cancer patients should be substantially revised, since it impairs patients’ quality of life and frequently fails to significantly extend survival (3). The development of more “intelligent” drugs targeting specific molecular pathways may significantly improve the outcome of advanced cancer patients during the next decade. However, the focus of researchers and clinical oncologists is currently shifting from exclusively targeting cancer cells to a more comprehensive approach which also includes supportive therapies for the host.

One of the major limitations of current pharmacological anti-cancer therapies is the development of toxicity, which frequently leads to dose limitation and interruption of the treatment schedule (4). However, of specific concerns for nutritional care specialists is the evidence that anticancer therapies directly impact on cancer patients’ nutritional status, which in turn exacerbates toxicity. Therefore, the development of new strategies limiting toxicity, allowing for complete delivery of antineoplastic therapies and improving patients’ quality of life is warranted. However, it is unlikely that such goals could be soon achieved by new drugs, since the time needed to devise and test a new pharmacological agent may extend over a decade. Also, there is growing evidence of medical excess in rich countries, with increasing harms and costs (5) which could be further exacerbated by the “medicalization” of supportive care. Of more clinical relevance would be the implementation of strategies already widely available. In this light, nutrition could be of significant help (6).

2. Anticancer Therapies and Nutritional Status

2.1 Nutritional Status and Cancer Treatment Toxicity

Cancer treatment toxicity results not only from the pharmacological properties and the delivered dose of any given drug. Indeed, other non-preventable and preventable factors play a significant role as well. As an example, individual genetic background has been repeatedly demonstrated to predict toxicity of radio- and chemotherapy (7, 8). On the other hand, cancer-induced malnutrition, i.e., cachexia, is tightly related to the development of complications of antineoplastic regimens. In particular, sarcopenia, which is the hallmark of cancer cachexia (9), predicts dose-limiting toxicity (10), post-operative complications (11) and survival (12) of patients with tumours of different origins and receiving different antineoplastic therapies. Therefore, prevention or restoration of muscle mass in cancer patients may well result in better tolerance and improved compliance to antineoplastic regimens. It should be noted that cancer cachexia is a multifactorial syndrome and different factors contribute to its pathogenesis. Moderate yet chronic tumour-induced inflammatory
response, reduced appetite and food intake, and impaired muscle anabolism due to reduced physical activity are just a few pathogenic mechanisms (13). Therefore, effective prevention and treatment of cancer cachexia should be based on a multimodal and individualized approach, targeting as many causative factors as possible (13).

The tumour-induced inflammatory response can be blunted by diet modification, and in particular by increasing the intake of omega-3 polyunsaturated fatty acids (PUFAs), namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). After being incorporated in the lipid layers of cell membranes, omega-3 PUFAs are metabolized by cyclooxygenase and lipoxygenase yielding the production of eicosanoids, namely thromboxanes and prostaglandins, whose pro-inflammatory activity is less potent than that mediated by eicosanoids derived from omega-6 PUFAs. In fact, cancer patients supplemented with omega-3 PUFAs showed reduced levels of arachidonic acid-derived prostaglandin E₂ when compared to patients receiving a standard, not omega-3 PUFAs enriched, supplement (14). More importantly, a recent clinical trial demonstrated that cancer patients supplemented with an omega-3 PUFA enriched product during active treatment for lung cancer had better physical function than patients receiving a standard supplement (15). This evidence shows that in clinical practice, nutrition-mediated amelioration of the inflammatory response translates into clinically relevant outcomes. Further supporting the relevance for cancer patients of omega-3 PUFAs supplementation, Deutz et al. showed restored muscle anabolism by a specially designed medical food which includes omega-3 PUFAs (16). It is therefore becoming widely acknowledged that nutrition interventions in cancer patients contribute to achieve important patient-centered outcomes, including better quality of life (17), reduced late toxicity and extended survival (18), particularly when combined with the other pillars of palliative care, i.e., psychological support and pain control (19).

Although these evidence are compelling, it should be noted that the population involved in studies addressing the role of nutrition on cancer patients’ outcome is still limited and therefore the robustness of the results obtained may not be sufficient to strongly recommend the implementation of palliative care during active treatment. Nevertheless, considering the dramatic improvement of cancer patients’ outcome due to simple, cheap and already available treatments, i.e., nutritional care, psychological counselling and pain control, the American Society of Clinical Oncology issued a provisional clinical opinion, recommending the integration of nutritional care during active treatment for cancer (20). Therefore, early integration of palliative care into anticancer treatment is a procedure which is seen to benefit cancer patients in terms of better quality of life and extended survival (21).

### 2.2 Cancer Treatment Toxicity and Nutritional Status

Surgery remains a mainstay of cancer therapy, and it is frequently curative. However, aggressive surgical procedures may yield permanent, moderate to severe dysphagia (e.g., in patients operated for head & neck cancers) or reduced ability to digest and absorb nutrients (e.g., in patients operated for gastrointestinal cancers). A 10% loss vs pre-surgery body weight is considered almost unavoidable after extensive gastrointestinal resection. Therefore, nutritional status should be optimized before and carefully monitored after surgery. More importantly, nutritional care should be pro-actively implemented in the perioperative period, since this approach has been demonstrated to yield significant clinical benefits to cancer patients (18).
Chemotherapy and radiotherapy, particularly when they are delivered in combination, cause mucositis, nausea, vomiting, changes of taste and smell. These negative effects may last a few days or even weeks, and create a caloric/protein gap between daily requirements and intake. This may result in cyclical exacerbation of weight loss, which is frequently not restored when the toxic effects of chemo- and radiotherapy diminish. Sanchez-Lara et al. have shown in cancer patients under chemotherapy that changes of sweet detection threshold lead to significant alterations of caloric, protein and carbohydrate intakes, which may account for up to 500 Kcal/day (22). This evidence highlights the importance of intensive nutritional surveillance and counselling during chemo- and/or radiotherapy.

Beyond the nutritional impact of their side effects, some anticancer drugs may directly impact on muscle mass. In an experimental model, van Norren et al. showed that doxorubicin induces impaired ex vivo skeletal muscle relaxation, followed in time by contraction impediment, which may contribute to the onset of the clinical syndrome of fatigue (23). More recently, Antoun et al. showed that muscle loss is a sorafenib-related adverse effect that may relate to asthenia, fatigue, and physical disability, which in turn limit the ability to practice physical activity, a potent anabolic stimulus (24). This evidence highlights the importance of considering a pre-emptive nutritional strategy in those patients scheduled to receive drugs which are known inducers of muscle loss and functional impairment.

3. Specific Nutrients and Tumour Growth

There is accumulating evidence that nutritional support improves cancer patients’ outcome by preserving/restoring nutritional status. However, it is tempting to speculate that nutrition may also directly influence tumor growth. Many examples exist in Nature showing that animals use food to prevent and treat diseases (25), an ability which has been lost by humans.

The mechanisms of tumour initiation and growth have been extensively investigated, and the “seed and soil” theory is now widely accepted. According to this hypothesis, tumour initiation, promotion and invasiveness are due not only to the intrinsic genetic and metabolic features of cancer cells. Indeed, the environment where cancer cells develop plays a similarly important role. Cancer cells require an inflammatory microenvironment to proliferate and disseminate (26) since chronic inflammation reduces host immune surveillance (27). Supporting this view, it is well established that malignancy and aggressiveness of human cancers are related to the degree of stromal infiltration by inflammatory cells (28). Consequently, neutralizing the tumour’s inflammatory microenvironment, or boosting host immune surveillance, may represent effective strategies to enhance the response rate of cancer patients to chemo- and radiotherapy (29).

Arginine is an amino acid which has been extensively demonstrated to increase the immune response, and therefore its use could be beneficial in cancer patients. Indeed, Buijs et al. showed that patients with head and neck cancer receiving an arginine-enriched enteral formula in the perioperative period had a longer survival that those receiving a standard formula (30).

EPA and DHA, by neutralizing inflammatory response within the tumoural microenvironment, may restore host immune competence and favour tumour rejection. Also, by incorporation in cancer cell membranes, EPA and DHA may enhance the antitumour activity of standard
chemotherapy. Bougnoux et al. demonstrated in patients with advanced breast cancer that DHA supplementation during chemotherapy prolongs survival in high omega-3 PUFA incorporators (31). Similarly, Murphy et al. showed that EPA supplementation during active treatment for advanced lung cancer almost doubles the clinical response rate (2).

More recently, a specific metabolic pathway of DHA which is distinct from those involved in the production of eicosanoids, has been demonstrated to exert potent anti-tumour activity. As previously mentioned, fatty acids are mainly metabolized by cyclooxygenase and lipoxygenase, however, they also represent the substrate for cytochrome P450, being then transformed into epoxy metabolites. Recent data showed that the epoxy metabolites of DHA have potent anti-tumour activity in vitro (32). In vivo, pharmacological inhibition of the degradation of epoxy metabolites of DHA results in reduced angiogenesis, tumour growth and metastasis in an experimental cancer model (32).

These results, although in need of further strength by larger trials, show that nutrition may directly influence tumour growth or enhance chemotherapy efficacy, beyond its impact on nutritional status.

4. Caloric Restriction and Differential Stress Response in Oncology

Based on animal data (33), it has been proposed that in healthy individuals caloric restriction (i.e., 20-40% reduction of daily energy intake without causing malnutrition) may prevent the onset of chronic diseases and extend lifespan (34). The relevance of caloric restriction has been recently challenged (35) and it is now generally acknowledged that protective cellular responses could be triggered by provision/restriction of specific nutrients, rather than non-selective caloric restriction. The concept of using specific nutrients to evoke differential stress response may well apply to cancer patients, in whom caloric restriction appears unsuitable since it may exacerbate malnutrition (36). Supporting this approach, recent studies show that selective serine starvation reduces tumour growth and extends survival of tumour-bearing animals (37). Also, a ketogenic diet, i.e., a severely carbohydrate-restricted diet, has been reported to effectively enhance the efficacy of radiation therapy for the treatment of experimental malignant glioma (38). Anecdotal reports seem to validate the relevance of ketogenic diets also in brain cancer patients (39).

It is therefore tempting to speculate that specifically designed diets, delivered at critical timepoints in the clinical journey of cancer patients, may trigger differential stress responses in normal and cancer cells, favouring the cytotoxic effects of chemo- and radiotherapy on the tumour while increasing resistance of normal cells, ultimately leading to tumour rejection.

5. Conclusions

Nutrition is not a mere source of calories and nitrogen. Specific nutrients have been shown to re-programme gene expression and re-direct human metabolism. It is therefore key that nutrition support is integrated early in the multimodal approach to cancer patients, in order to prevent or treat cancer cachexia, but also to prime patients’ metabolism and favour rejection of cancer cells.
6. Summary

Cancer remains one of the leading causes of morbidity and mortality, and a major contributor to the increasing costs of healthcare. Cost-effectiveness of anti-cancer therapies is suboptimal, since cancer treatment toxicity contributes to ineffective delivery of chemotherapy and radiotherapy. Muscle mass is a key predictor of toxicity, and therefore timely provision of nutritional and metabolic support to cancer patients may prevent muscle wasting and increase resistance to cancer treatment toxicity. Also, specific modulation of nutrient intake in the peri-chemotherapy period may induce differential stress responses of normal and tumour cells, the former becoming more resistant to the side effects, and the latter more susceptible to chemotherapy. Exploiting the pharmacological effects of specific nutrients may also be clinically relevant. Inflammatory infiltration of the tumour microenvironment has been demonstrated to increase cancer aggressiveness. Consequently, modulation of the inflammatory microenvironment may result in improved efficacy of chemotherapy. Recent data show that fish oil or arginine supplementation to cancer patients during active treatment results in improved outcome. When considered together, these results suggest that the efficacy of chemotherapy and radiotherapy can be enhanced by integration of pharmaconutrition.

7. References

5. Godlee F. Too much medicine. BMJ 2013; 346:f1328