Is Immune Nutrition the Holy Grail for Cancer Patients?

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The limited benefit, if any, of standard parenteral (PN) or enteral nutrition (EN) in cancer patients has led to the concept that the quantity of nutrients may not be the only issue, and that qualitative modulation of nutritional substrates could restore the nutritional and immunological status of the host, without enhancing tumor growth. Ideally, such substrate supplementation, or depletion, should enhance immunological defences, replete protein stores in the host, and sensitize the tumor to specific treatments. We will address certain aspects of pharmacological/immunological nutrition, with special emphasis on glutamine, arginine, ω-3 fatty acids and growth factors [1–4].

Is Glutamine Supplementation Beneficial to Tumor-Bearing Patients?

Glutamine, the most abundant amino acid in the body, is a preferential substrate of rapidly dividing cells and tissues _in vivo_, such as lymphocytes, macrophages and intestinal epithelial cells, and is also mandatory for optimal _in vitro_ cell culture [5]. Unfortunately, glutamine is also actively consumed by tumors, in both animals and humans. High levels of glutaminase, the first-step enzyme of glutamine metabolism, have been reported in rapidly growing tumors, with a striking negative correlation between glutaminase activity and the tumor doubling time.
This glutamine trap, and the metabolic alterations mediated by tumor-secreted mediators [6] and cytokines [7], results in a severe imbalance in glutamine homeostasis. Despite accelerated glutamine release from enhanced muscle protein breakdown and from the lungs, the gradual glutamine depletion of the host leads to a reduced glutamine supply to the gut and immune cells. This leads to host glutamine depletion, which has adverse effects on gastrointestinal mucosal integrity and favors the occurrence of infectious complications and poor tolerance of antineoplastic treatments [8].

Given the avidity of tumors for glutamine, it has been proposed to “fast” the tumor either by using exogenous glutaminase, or by giving glutamine analogs acting as antagonists (e.g. acivicin) of the first metabolic step. Although some tumor growth inhibition has been reported, especially with combined acivicin and insulin therapy, experimental and clinical results are globally disappointing and offset by unacceptable toxicity, especially in the form of severe mucositis and reversible, dose-limiting CNS toxicity, characterized by lethargy, confusion and poor mental status [9].

In an alternative concept glutamine supplementation is expected to support immune [10], muscle and gut functions [11], reduce infectious complications and improve tolerance of antitumor therapy. This assumes that glutamine is primarily beneficial to the host and causes only minor stimulation of tumor growth, if any. The influence of glutamine supplementation on tumor growth in vivo has been evaluated in tumor-bearing animals [1]. In most cases the anabolic affect on muscle was confirmed by a significant increase in carcass weight and no significant influence on tumor weight. Glutamine supplementation of tumor-bearing animals has been reported to support gut function (small bowel protein content or jejunal protein synthesis rate) without affecting tumor growth [12]. Finally, glutamine enhanced the activity of natural killer lymphocytes (one of the main lines of defense against tumor cells) in vitro and in vivo, and it has been suggested that the beneficial effects of glutamine on tumor growth may be related to a modulation of glutathione metabolism, as also postulated in critically ill patients [13].

The gastrointestinal toxicity of radiation therapy and anticancer drugs such as methotrexate and 5-fluorouracil results from direct damage to the rapidly proliferating intestinal epithelium. Thus, glutamine provision might be expected to preserve gut integrity or enhance its recovery after injury. In various animal models of drug- or radiation-induced enteritis or enterocolitis, various amounts and combinations of glutamine were delivered by the enteral or parenteral route. On the whole, enteral glutamine supplementation reduced the severity of both drug-induced [14] and radiation-induced [15] enterocolitis, maintained intestinal barrier function (reduced bacterial translocation) and resulted in a decrease in mortality [16]. However, most studies dealt with otherwise healthy, i.e. nontumor-bearing, animals. In addition, intravenous administration of glutamine seemed to be ineffective in the same models. In tumor-bearing animals, intestinal extraction of circulating glutamine across the basolateral membrane is reduced, while uptake
Is Immune Nutrition the Holy Grail for Cancer Patients?

from the intestinal brush border is increased [17]. Last but not least, it must be kept in mind that the long-term effects of supplementation on the efficacy and tolerance of treatments are unknown, as are the potential effects on the survival of tumor-bearing animals.

As oral or enteral glutamine supplementation is thought to be preferable to parenteral administration [18], the effect of oral glutamine on chemotherapy-induced toxicity has been explored in several clinical studies. Short-term fractionated oral administration of a relatively low dose of glutamine (16 g/day) in patients with advanced gastrointestinal cancer, during one course of 5-fluorouracil and leucovorin combination therapy, had no significant effect on the mucositis score [19]. In contrast, a suspension of L-glutamine (4 g “swish and swallow” twice a day), given from day 1 of chemotherapy for 28 days, resulted in a significant decrease in the duration of mouth pain (4.5 days), and in the total number of days with mucositis (4 days) in 24 patients in a similar cross-over study [20]. The same group compared glutamine with a placebo (glycine) from admission until day 28 in 193 bone marrow transplantation (BMT) patients in a randomized, double-blind, placebo-controlled study. In 87 autologous BMT patients glutamine administration resulted in significantly less mouth pain, whereas the 106 matched sibling BMT patients had a significantly increased duration of opiate use, possibly due to interaction with methotrexate. However, survival of allogeneic patients at 28 days was improved by glutamine. No significant differences in TPN use, parenteral antibiotic use, acute or chronic graft-versus-host disease, or length of hospital stay were observed in either autologous or allogeneic recipients [21]. In addition, oral glutamine supplementation was recently found to be effective on arthralgias and myalgias during chemotherapy containing paclitaxel [22].

In patients undergoing BMT for hematologic malignancies, supplementation of PN with either free glutamine or glutamine-containing dipeptides gave controversial results. In the study by Ziegler et al. [23], patients received either a standard or a glutamine-enriched formula providing 0.57 g of free glutamine/kg/day. Not only was the nitrogen balance significantly less negative in the glutamine-supplemented group, with a parallel reduction in 3-methylhistidine urinary excretion, but the incidence of infectious complications and the duration of hospital stay were also significantly reduced [23] (Table 1), with a clear improvement in mood and a valuable cost reduction in the treated group [24]. A similar reduction in hospital stay was reported by Schloerb and Amare [25], although a statistically significant reduction in infectious complications was only found in the subgroup of patients undergoing allogeneic transplantation. Conversely, Van Zaanan et al. [26] failed to find any beneficial effect of glutamine-supplemented PN in a heterogeneous group of hematologic patients. More recently, Bozzetti et al. [27], in an elegant double-blind study involving 65 patients with advanced breast cancer, found that glutamine (30 g/day) neither prevented the occurrence of doxorubicin-induced diarrhea nor had any impact on the tumor response to chemotherapy.
Table 1. Metabolic and outcome variables after glutamine-supplemented (0.57 g/kg/day) total parenteral nutrition (TPN) for bone marrow transplantation (means ± SE)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard TPN (n = 21)</th>
<th>Supplemented TPN (n = 24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrogen balance, g/7 days</td>
<td>−29.6 ± 8.6</td>
<td>−9.7 ± 3.4</td>
<td>0.002</td>
</tr>
<tr>
<td>3MH/creatinine ratio</td>
<td>13.3 ± 0.9</td>
<td>10.9 ± 0.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Total ATB, days</td>
<td>44 ± 8</td>
<td>39 ± 7</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sterile cultures</td>
<td>1</td>
<td>10</td>
<td>0.005</td>
</tr>
<tr>
<td>Positive stool cultures</td>
<td>16</td>
<td>10</td>
<td>0.034</td>
</tr>
<tr>
<td>Positive throat cultures</td>
<td>18</td>
<td>13</td>
<td>0.028</td>
</tr>
<tr>
<td>Clinical infections</td>
<td>9</td>
<td>3</td>
<td>0.041</td>
</tr>
<tr>
<td>Length of stay, days</td>
<td>36 ± 2</td>
<td>29 ± 1</td>
<td>0.017</td>
</tr>
</tbody>
</table>

3MH = 3-Methylhistidine; ATB = antibiotics. Adapted from Ziegler et al. [23].

Thus, the clinical benefits of glutamine-enriched nutrition have to be confirmed in various types of cancer [28]. In addition, the potential stimulation of tumor growth by glutamine cannot be ruled out, suggesting that further clinical studies of glutamine supplementation in cancer patients should include a careful assessment of tumor kinetics, to comply with ethical requirements.

### Ornithine α-Ketoglutarate and Cancer

Ornithine α-ketoglutarate (OKG) is a very old product but its anabolic properties (stimulation of insulin and growth hormone (GH) secretion) and anticatabolic properties (stimulation of glutamine and arginine synthesis) [29] are theoretically adapted to catabolic illnesses such as cancer (Fig. 1). OKG is easy to administer, enteraly or parenterally, over 24 h or, preferably, in short infusions [30]. Some authors have found that OKG is as effective as glutamine for the maintenance of muscle ribosome and polyribosome levels, apparently reflecting a sparing effect on muscle protein synthesis capacity [31]. In animal models, OKG metabolism led to enhanced amounts of arginine and glutamine in skeletal muscle, adaptive hyperplasia of the villi via γ-aminobutyric acid formation in the intestinal mucosa, and an increase in brush-border hydrolase activities [32]. OKG administered to rats with burn injuries had immunomodulatory properties that enhanced host defense mechanisms [33]. A clinical benefit was recently shown in severe burn patients, who had a better quality of wound healing after skin grafts while on enteral OKG supplementation [34]. In a controlled study of rats receiving either OKG or an equivalent amount of nitrogen after abdominal irradiation,
Is Immune Nutrition the Holy Grail for Cancer Patients?

Fig. 1. Metabolic pathways of ornithine α-ketoglutarate.
Ornithine α-ketoglutarate possesses anabolic properties via the stimulation of insulin and GH secretion, and anticatabolic properties via the stimulation of glutamine and arginine synthesis that are theoretically adapted to the hypermetabolic states. Ornithine is a precursor of polyamines that are essential for cell growth and protein synthesis.

OKG was found to accelerate healing of the small intestine, as shown by more rapid recovery of normal villous architecture, and to reduce bacterial translocation to the level observed with a normal chow diet [35].

OKG supplementation of rats with implanted hepatomas had no influence on tumor progression, while it significantly reduced protein breakdown measured ex vivo [36, 37]. To match the clinical situation in which tumor burden is small at diagnosis and at initiation of treatment, diets containing OKG or an isonitrogenous, isocaloric diet containing glycine were tested in rats treated by tumor excision at a limited stage of the disease. By comparison with glycine-fed rats, OKG-fed rats had a more positive nitrogen balance, higher concentrations of muscle glutamine, and accelerated protein deposition in the small intestine (p < 0.05) [37]. These results may explain the failure of nutritional support in untreated cancer and underline the need for clinically relevant animal models.

However, in spite of these exciting new effects of OKG supplementation on protein metabolism and immunoregulation in tumor-bearing animals, the potential value of OKG administration to cancer patients must still be confirmed.
Pharmacological Nutrition with Arginine

Arginine is a specific example of a nutrient with immunomodulatory potential [38]. It is a semi-essential amino acid in adults and becomes indispensable when its endogenous synthesis is inadequate, as in cancer. Apart from its role in urea and protein (collagen) synthesis and as a stimulant of several endocrine secretions [insulin, GH and insulin-like growth factor-1 (IGF-1), among others], arginine has been found to have several immunomodulatory actions [39], such as accelerated wound healing and stimulated thymus growth, lymphocyte proliferation and mononuclear cell responses to mitogens; it also enhances lymphokine-activated killer cell generation via a nitric oxide (NO)-mediated mechanism, and stimulates the release of polyamines by the small bowel [40]. These immunostimulant effects of arginine have been shown in several animal studies with experimentally induced infections or trauma [41].

Although the mechanisms responsible for the immunomodulatory effects of arginine are unclear, it is likely that NO generated from arginine by the action of NO synthase is the major pathway [42]. Indeed, the in vivo tumoricidal activity of peritoneal macrophages on transplanted cancer cell lines is significantly reduced by the administration of the NO synthase inhibitor LMNA [43]. However, the situation is not that simple: Xie et al. [44] demonstrated that inducible NO synthase (iNOS) expression in tumor cells was associated with apoptosis, suppression of tumorigenicity, abrogation of metastasis, and regression of established hepatic metastases. It is well known that non metastatic cancer cells exhibit a high level of iNOS activity and NO production, whereas metastatic cells do not [44].

The antitumoral effects of arginine have been observed in most animal models of chemically induced or transplanted tumors [1]. However, while supplementation with 1% arginine significantly enhanced thymus weight gain and the natural killer cell activity [45], higher doses of arginine tended to inhibit the in vitro immune response, as in animal models of sepsis [46]. In another model, the combination of arginine and interleukin-2 stimulated activated killer cell activity, limited tumor growth and improved survival, while arginine alone had no effect [47]. In contrast, some authors have reported that tumor growth may be limited by arginine privation in a murine model of colon cancer [48]. The role of arginine is thus controversial, together with the part played by NO in the underlying mechanism of action. Furthermore, animal studies show the importance of determining the optimal dose, as excessive doses may be harmful. The complexity of the problem was illustrated by Edwards et al. [49], who reported that the arginine concentration influenced the growth of some types of tumor cells in vitro and that dietary arginine supplementation augmented tumor growth in vivo. The mechanism of tumor growth modulation is NO-dependent in vitro but not in vivo [49].

The potential benefits of supplemental arginine in cancer patients are poorly documented. In patients with breast cancer, Park et al. [50] found a stimulation of protein synthesis after 3 days of arginine-supplemented feeding. These findings
are in marked contrast with most of the above animal data, but may be explained by differences in the doses and the resulting plasma arginine concentrations. In addition, stimulation of proliferation may be beneficial if it sensitizes the tumor to the action of antimitotic drugs or host defenses, as suggested by Brittenden et al. [51], who showed that dietary supplementation with arginine in patients with breast cancer significantly increased lymphocyte mitogenic reactivity as well as natural killer and lymphokine-activated killer cell cytotoxicity. Finally, Caso et al. [52] recently showed that arginine supplementation for 3 days before surgery for head and neck cancer did not enhance tumor protein synthesis, suggesting that arginine supplements are safe in this type of cancer.

In summary, available data on the use of arginine for immunonutrition of cancer patients are mainly experimental, with controversy over the optimal dose and route with respect to the type and immunogenicity of the tumor. Clinical studies on the safety and efficiency of arginine in the clinical setting of cancer are urgently needed.

**Immunomodulatory Effect of Polyunsaturated Fatty Acids**

The immunomodulatory effects of new lipid formulations may be useful in cancer patients. As essential fatty acids are the sole precursors of eicosanoids, the former may alter the rate of eicosanoid production, which in turn modulates the immune response [53]. The induced alterations of membrane phospholipids affect cell functions and membrane fluidity [54]. Conventional lipid emulsions are relatively rich in ω–6 polyunsaturated fatty acids (PUFAs; linoleic and arachidonic acids); the breakdown of arachidonic acid leads to increased dienoic prostaglandin (PG) and thromboxane (TB) production, e.g., PGE₂ and TBA₂, and increased tetraenoic leukotriene (LT) production, e.g., LTB₄, which are mainly responsible, particularly in macrophages, for their immunosuppressive properties and for the generation of free oxygen radicals (Fig. 2). In contrast, such emulsions are poor in ω–3 PUFAs (linolenic acid) which inhibit the breakdown of arachidonic acid via the cyclooxygenase pathway and, thus, the synthesis of PGE₂; they lead, via the eicosapentaenooids, to trienoic PGS, e.g., PGE₃ and PGI₃, and TBA₃, and to pentaenoic LTs, e.g., LTB₅. ω–3 PUFAs therefore give rise to a decrease in platelet activation and thrombogenesis, and inhibit the inflammatory reactions related to the activation of target cells by cytokines [55].

ω–3 fatty acids have protective effects on the development of carcinogen-induced tumors, the growth of solid tumors, cachexia, and metastatic diseases in experimental models [56]. It appears that the metastatic process can effectively be reversed in vivo by eicosapentaenoic acid, but not by other PUFAs of either the ω–3 or ω–6 series [57, 58]. However, other studies have given conflicting results: in rats kept on either a low-fat diet or on a fish oil (ω–3 PUFAs) or sunflower oil (ω–6 PUFAs) diet for 3 weeks before being challenged with colon cancer cells via the
Fig. 2. Metabolic pathways of ω-3 and ω-6 polyunsaturated fatty acids (PUFAs). 
Free arachidonic acid (AA) and eicosapentaenoic acid (EPA) are respectively released from membrane macrophage phospholipids by the action of phospholipases A2 and C. Free AA and EPA are rapidly metabolized through two main pathways involving the action of lipooxygenase and cyclooxygenase. Prostanoids are synthetized by cyclooxygenase; leukotrienes (LTs) are formed by lipooxygenase. AA, via both these pathways, yields superoxides and is thought to be mainly responsible for the immunosuppressive properties of ω-6 PUFAs. EPA leads to trenoic prostaglandins (PGs) and pentaenoic LTs that are supposed to decrease platelet activation and to inhibit the inflammatory reaction. PAF = Platelet-activating factor; TNF = tumor necrosis factor; IL = interleukin; TB = thromboxane.
portal vein, ω–3 and ω–6 PUFAs promoted colon cancer metastasis in the liver without downregulating the immune system [59]. This could indicate that levels of dietary fat, regardless of their composition, play a role in cancer proliferation [60].

Dietary supplementation with ω–3 fatty acids has been tested in several clinical trials. In pancreatic cancer, a malignancy associated with a persistent inflammatory response and increased energy expenditure, three months of dietary supplementation with a median of 12 g/day fish oil (eicosapentaenoic acid 18% and docosahexaenoic acid 12%) led to a significant median weight gain of 0.3 kg/month, accompanied by a temporary but significant reduction in acute-phase protein production and by stabilization of resting energy expenditure [61]. Gogos et al. [62] randomized 60 patients with generalized solid tumors to dietary supplementation with either fish oil or a placebo daily until death. ω–3 PUFAs had an impressive immunomodulating effect, as reflected by the T-helper/T-suppressor cell ratio, in the subgroup of malnourished patients. There were no significant differences in cytokine production among the various groups. In addition, ω–3 fatty acids prolonged the survival of all the patients [62].

These stimulating results warrant further clinical trials to establish the exact benefits and limitations of ω–3 PUFA supplementation in cancer patients.

**Hormones, Insulin and Growth Factors**

Several attempts have been made to reverse muscle protein breakdown by means of hormones such as insulin, GH, IGF-1, and anabolic agents. The main danger of this approach is to stimulate tumor growth. Interesting perspectives for future clinical trials can be derived from experiments in tumor-bearing animals.

Ng et al. [63] examined the anabolic properties of GH that preserved normal body composition in sarcoma-bearing animals treated with doxorubicin. The treated group had a significantly higher body and carcass weight, total fat-free body mass, IGF-1 and GH plasma levels than the control group. There was no difference in final tumor weight or the tumor growth rate between the two groups. Thus, GH can attenuate weight loss and preserve lean body mass in tumor-bearing animals without stimulating tumor growth [64]. In the same way, a simultaneous combination of GH and IGF-1 had a favorable anabolic effect on the host, with no major increase in the relative tumor burden [65]. Studies of insulin monotherapy of cancer cachexia have had limited success, due to insulin-induced hypoglycemia and subsequent glucagon secretion. Bartlett et al. [66] reported that blockade of endogenous hormonal secretion by somatostatin and exogenous supply of insulin and GH significantly improved skeletal muscle protein content and reduced protein incorporation by the tumor in rats with MAC-33 mammary adenocarcinoma. However, as usual, there is a long way from the bench to the bedside. According to Lazarus et al. [67], neither IGF-1 nor insulin had any effect on the cachexia associated with colon-26 tumors in mice.
Is Immune Nutrition the Holy Grail for Cancer Patients?

### Table 2. Main characteristics of immune-enhancing diets

<table>
<thead>
<tr>
<th></th>
<th>Impact</th>
<th>Immun-Aid</th>
<th>AlitraQ</th>
<th>Stresson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, cal%</td>
<td>22</td>
<td>32</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Free glutamine, g/l</td>
<td>0</td>
<td>12.5</td>
<td>14.2</td>
<td>13</td>
</tr>
<tr>
<td>Arginine, g/l</td>
<td>14.0</td>
<td>15.4</td>
<td>4.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Nucleotides, g/l</td>
<td>1.25 + RNA</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lipids</td>
<td>palm, safflower, and menhaden</td>
<td>Canola, MCT</td>
<td>safflower, MCT</td>
<td>vegetable + fish</td>
</tr>
<tr>
<td>ω–3 fatty acids, g/l</td>
<td>1.68</td>
<td>1.1</td>
<td>–</td>
<td>30 mg</td>
</tr>
<tr>
<td>Antioxidants</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>vitamins A, C, E</td>
</tr>
</tbody>
</table>

MCT = Medium-chain triglyceride; LCT = long-chain triglyceride.

Finally, administration of β2-adrenergic agonists to tumor-bearing rats resulted in partial recovery of skeletal muscle and heart mass [68]. Treatment of tumor-bearing animals with salbutamol, salmeterol and clenbuterol did not influence tumor growth. Any of the three β2-adrenergic agonists, but particularly salmeterol, should be evaluated clinically in the treatment of cancer cachexia.

**Immune Diets: Do Combinations of Several Immune Nutrients Resolve the Problem?**

The enrichment of nutrient mixtures with arginine and vitamin C, a reduction in ω–6 PUFAs and enrichment with ω–3 PUFAs, all considered to be immunomodulatory, has given interesting results in animal models and is currently under clinical investigation [2, 4, 69]. The novel concept of “nutritional pharmacology” or “immune-enhancing nutrition” underlies the development of four specific enteral formulas commercially available (Impact, Sandoz Nutrition; Immun-Aid, McGaw Inc.; AlitraQ, Ross Laboratories, and Stresson, Nutricia Laboratories) to modulate the inflammatory and immune response to tissue injury. The PUFA, arginine and purine content of the formulations is modified, while still providing nutritional support for immunocompromised patients (Table 2). At present, only Impact has been studied in randomized, prospective clinical trials, utilizing early enteral feeding techniques, and compared to patient-related outcomes. In the context of cancer, all the available data come from studies performed in surgical oncology. No such studies are currently available in medical (chemotherapy or radiotherapy) oncology.

The immunostimulant effect of Impact was evaluated in several well-designed studies devoted exclusively or partially to cancer patients [70–72]. Although these
Is Immune Nutrition the Holy Grail for Cancer Patients?

Fig. 3. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients.
When combining wound complications with the occurrence of infection, Impact was superior to the control diet ($p < 0.05$). Mean length of stay was also reduced in the Impact group.
The baseline mortality rate was very low in both groups. It is noteworthy that 94% of the patients randomized to receive long-term tube feeding completed their postoperative chemoradiation therapy, whereas 61% not randomized to tube feedings required cross-over to jejunostomy nutritional support. Adapted from Daly et al. [74].

studies evaluated variations of a broad range of immune and inflammatory parameters retrospectively, the overall results favored the use of Impact over the standard control nutrition.

With regard to clinical effectiveness, an increasing number of randomized double-blind studies are available (Table 3). In the study by Daly et al. [73], 85 patients having undergone major surgery for gastrointestinal (GI) malignancies received postoperative EN with either Impact or Osmolite HN. There was no difference between the two groups with regard to the length of hospital stay in the intention-to-treat analysis. Likewise, there was no significant reduction in individual infections (such as pneumonia) in the Impact group, but when the various infectious complications were combined with anastomotic dehiscence, the difference became statistically significant in favor of Impact. This result was confirmed by another similar study from the same group [74] (Fig. 3). Comparison of the three studies by Heslin et al. [78], Senkal et al. [77] and Braga et al. [80] is intriguing. All three evaluated the effects of Impact in the postoperative period of major surgery in a large population of GI cancer patients, but the three study designs differed notably. Schematically, Senkal et al. [77] compared Impact with an isocaloric, isonitrogenous placebo, while Braga et al. [80] added a third group receiving
Table 3. Prospective, randomized, clinical trials of immunonutrition in cancer surgery

<table>
<thead>
<tr>
<th>Reference, year</th>
<th>Patients and diet(s)</th>
<th>Isocaloric, isonitrogenous</th>
<th>Results, statistical significance</th>
<th>Efficacy? comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heslin et al. 1997 [77]</td>
<td>GI surgery (n = 154) Impact vs. Std</td>
<td>Yes</td>
<td>No difference for minor and major complications, LOS and mortality</td>
<td>No 61% (Impact) and 22% (Traumacal) of energy requirements. Provocative study and results</td>
</tr>
<tr>
<td>Schilling et al. 1996 [76]</td>
<td>GI surgery (n = 41) Impact (A) vs. Std (B) and low-lipid diet (C)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Kenler et al. 1997 [75]</td>
<td>GI surgery (n = 50) FOSL-HN vs. Osmolite HN</td>
<td>Yes</td>
<td>m Infections (NS)</td>
<td>No</td>
</tr>
<tr>
<td>Gianotti et al. 1997 [79]</td>
<td>GI surgery (n = 260) Impact (A) vs. Std vs. TPN</td>
<td>Yes</td>
<td>% Infections: A &lt; Std &lt; TPN (p = 0.06) Hospital LOS: A &lt; Std (p = 0.01) &lt; TPN (p = 0.004)</td>
<td>Yes</td>
</tr>
<tr>
<td>Braga et al. 1998 [80]</td>
<td>GI surgery (n = 166) Impact (A) vs. Std vs. TPN</td>
<td>Yes</td>
<td>Infections, sepsis score and LOS (NS) in the Impact group</td>
<td>±</td>
</tr>
<tr>
<td>Braga et al. 1999 [81]</td>
<td>GI surgery (n = 206) Impact vs. Std</td>
<td>Yes</td>
<td>Infected patients, antibiotic days, LOS (all p &lt; 0.01) in the Impact group</td>
<td>Yes, but... Similar mortality (close to 0%) Similar incidence of infections??</td>
</tr>
<tr>
<td>Snyderman et al. 1999 [82]</td>
<td>Head and neck surgery (n = 136) Impact vs. Std</td>
<td>Yes</td>
<td>No differences in wound healing and LOS in the Impact group (modified ITT, n = 129; p = 0.02) Similar LOS and wound healing problems</td>
<td>No</td>
</tr>
</tbody>
</table>

GI = Gastrointestinal; Std = standard enteral formula; FOSL = fish oil structured lipid; HN = high nitrogen; IED = immune-enhancing diet; LOS = length of stay; ICU = intensive care unit; TNP = total parenteral nutrition; ITT = intent-to-treat.
Is Immune Nutrition the Holy Grail for Cancer Patients?

Fig. 4. Impact of route of administration and composition of the diet after major abdominal surgery. Impact was compared with an isocaloric, isonitrogenous enteral diet after gastrointestinal cancer surgery, and a third group received equivalent total parenteral nutrition (TPN). There is slight clinical advantage of enteral nutrition (EN) over TPN, and this advantage could be increased by the use of an “immune diet”, especially in severely malnourished patients and patients with multiple blood transfusions. However, the rate of postoperative infections and the length of stay in the intensive care unit do not differ between the three groups. From Braga et al. [80].

equivalent TPN, and Heslin et al. [78] challenged the dogma of obligatory postoperative nutrition by comparing Impact with simple postoperative hydration. The only convincing conclusion is that the concept of postoperative TPN is on the wane. The authors’ conclusions diverged, no doubt because of the methodological biases of each study: (a) in the study of Senkal et al. [77], only late infectious complications, after the 5th day, were fewer in the Impact group (5 vs. 13; p < 0.05) and a sound medico-economic evaluation showed a saving of approximately 22,000 Euros/150 patients; (b) Braga et al. [80] found a clear clinical advantage of EN over TPN, and suggested that this advantage could be increased by the use of an “immune diet” such as Impact, especially in severely malnourished patients and patients with multiple blood transfusions (p < 0.05), but the statistical analysis was questionable, particularly the analysis of variance (Fig. 4), and (c) finally, Heslin et al. [78] found no difference between the groups in terms of mortality, infectious morbidity or the duration of the hospital stay, but the effective calorie intake was only 61 and 22% of the calculated energy needs, respectively, in the Impact and hydration groups. Overall EN, or better immune-enhancing EN,
would appear to be effective only for particularly compliant patients, in GI cancer patients, except for patients with esophageal cancers, or would it be necessary for the first days to associate a complementary (immune?) PN? The most recent studies and meta-analyses do not permit elucidation of these problems, although the innovative study of Braga et al. [81] clearly suggests that a consistent efficacy of immunonutrition in GI surgery is firmly dependent on the preoperative administration of immunonutrients.

**Methodological and Ethical Considerations**

Apart from work directly aimed at correcting the most serious states of cachexia, most clinical trials of nutritional support in cancer have ended in failure. To solve this problem, sophisticated meta-analyses have been developed by statisticians, yielding a much more precise estimate of the therapeutic effect than provided by the individual studies. However, it should be stressed that the clinical trials selected for these meta-analyses, although similar, often differ significantly in terms of therapeutic regimens and the study populations. Yet tumors of different types and locations, with different effects on appetite and different risks of malnutrition, cannot reliably be subjected to identical criteria of analysis [83].

Outstanding questions can be summarized thus:

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Can nutritional support stop the course of cachexia, or even improve malnutrition, whatever the cause? Is there a link between the malnutrition resulting from GI obstruction and that due to the deleterious effects of the tumor on host metabolism?

Can the specific effects of anticancer treatments, especially chemotherapy and radiotherapy, be improved by new substrates in artificial nutrition?

Can artificial nutrition be beneficial to the patient without increasing tumor growth?

Are improvements in cost-benefit ratios on the one hand, and quality of life on the other hand, suitable goals in the nutritional management of cancer patients, taking into account the fact that nutritional support is usually regarded as “supportive care” rather than potentially curative? This point is fundamental.

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The improvement in quality of life by nutritional intervention is particularly difficult to prove, for two main reasons, one conceptual, the other practical. Conceptual difficulties can be overcome by refining and clarifying the definitions and indexes of quality of life [84, 85]. Practical difficulties are more complex and depend primarily on the characteristics of the underlying disease, the type of nutritional intervention, and the context in which the clinical trial is carried out. We must keep in mind that, in the present socioeconomic context, with increasingly scarce resources, quality-of-life assessment will undoubtedly become an essential element in the evaluation of all medical interventions [86]. They will
Is Immune Nutrition the Holy Grail for Cancer Patients?

make it possible to integrate the results of our future studies in an adequate and ethical evaluation of the costs and benefit of a treatment, taking into account improvements in both physical and mental well-being [87].

Conclusions

Many prospective randomized controlled trials have evaluated the role of PN and, to a lesser extent, of EN as adjuvant therapy of cancer. A clear benefit from nutritional support seems to be limited to a specific, small subset of patients. Research is currently directed toward a better understanding of the metabolic alterations in cancer patients, the definition of nutritional regimens that can efficiently support the host without promoting tumor growth, and on the impact of nutritional pharmacology on the host-tumor relationship. Glutamine, arginine, OKG, ω-3 fatty acids, nucleotides, antioxidants and growth factors are presently under extensive investigation. Glutamine-supplemented PN is probably beneficial in BMT patients. A recent meta-analysis suggests that immune diets reduce the rate of infectious complications and the length of hospital stay after GI surgery for cancer. In the future, carefully designed clinical trials are needed to determine the efficacy of such novel approaches in specific populations of cancer patients with an adequate definition of nutritional and oncological goals. Further studies should also address the question of the indications for conventional and immune-enhancing EN, of the overall cost-benefit ratio of nutritional pharmacology, and the effect of nutritional support on length and quality of life.

References

Is Immune Nutrition the Holy Grail for Cancer Patients?

Is Immune Nutrition the Holy Grail for Cancer Patients?


271
Is Immune Nutrition the Holy Grail for Cancer Patients?


Discussion

Dr. Baracos: I have a question about the prevalence of arginine deficiency, glutamine deficiency, and essential fatty acid deficiency in cancer patients. Where can I find the definitive work which will tell me what proportion of the patients are actually suffering from an overall deficiency of these nutrients?

Dr. Nitenberg: I think the idea about provision of immunonutrients is not to restore deficiencies but to add something to the conventional nutrition of the patient. The only deficiency you can see in aggressively treated cancer patients is of glutamine. There are some data in animals and in humans showing that glutamine stores in muscle and glutamine concentrations in the blood are very rapidly reduced and probably need to be restored [1]. But there is no deficiency of arginine and essential fatty acids in our usual diet. So the idea of giving these nutrients is to create a new environment. The aim is to increase the immune defenses in an artificial situation. I think it has now been proven that this is effective in clinical practice.

Dr. Baracos: For me, there’s something fishy about the arginine hypothesis. Starting with the animal literature, of about 16 papers dealing with supplemental arginine in animal models, eight claim increased tumor growth and eight claim decreased growth, and there is one that says there is no effect either way. In the glutamine literature, there are a few papers saying glutamine does not affect tumor growth and some saying it suppresses it, but you do not have a whole bunch of articles giving completely opposite results. This suggests to me that antitumor immunity has an arginine requirement, but tumor growth also has an arginine requirement. If both of those things have an arginine requirement, then if you give arginine you are influencing the balance of power. If that’s what is actually going on, which I suppose could be tested, I don’t see any way that you can predict, before giving the arginine, how that balance of power will emerge when you give the supplement, so that you will always have an equal chance of giving advantage to the host rather than to the tumor.

Dr. Nitenberg: This is a really good question, which means that it’s very difficult to answer. I totally agree with you. I’ve read your paper [2] and I found about 21 papers showing that arginine is effective and 19 showing that it is deleterious in animal models, so 50/50. Maybe we have to consider two different situations. When you give arginine as an immunonutrient in postoperative patients or maybe in patients after eradication of the tumor, the tumor is no longer there. In that case, arginine is used for its immune properties in stimulating the defenses of the organism. Indeed, there will be no problem of tumor growth in that case. It is a totally different situation when you give arginine while a tumor is present, whether the tumor is immunogenic or not. Clearly you will then increase protein synthesis both in the host and in the tumor, but in that case you could make the tumor more sensitive to cell cycle chemotherapy. This is a very intriguing idea, but unfortunately up to now no one appears to have followed it up with any published data.

References