Nutrition in Oncological Surgery

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Protein-energy malnutrition is commonly associated with cancer. About 50% of tumor-bearing patients present with various degrees of weight loss (WL) at the time of diagnosis. The paraneoplastic syndrome characterized by involuntary WL, anorexia, abnormal metabolism and tissue wasting is termed cancer cachexia.

Many cancer-related conditions are responsible for the development of cachexia, but in general it is possible to divide them into two main causes: reduced nutrient intake (or absorption), and metabolism imbalance.

Anorexia, learned food aversions and alterations in taste are frequent reasons for poor food intake; tumors of the gastrointestinal tract often produce obstruction, while oropharyngeal and esophageal cancers can cause odynophagia or dysphagia. Malabsorption sometimes occurs in the presence of pancreatic carcinoma causing exocrine insufficiency or in the case of bacterial overgrowth secondary to blind loop syndrome. Moreover, antineoplastic therapies may increase metabolic demands, produce gastro-intestinal toxicity and further interfere with nutrient intake or absorption. For instance, surgery can be complicated by prolonged ileus, infections and post-gastrectomy syndromes; chemotherapy is associated with nausea, vomiting, anorexia, altered taste, mucositis, stomatitis and diarrhea. Similar complications can also be induced by radiation therapy, depending on the site, dose and volume of tissue irradiated (Table 1).

In the normal subject, the physiological response to diminished food intake is a decrease in the resting energy expenditure (REE). In theory, all the above-mentioned conditions should induce in the patient the adaptive changes found in the
Table 1. Factors contributing to cancer cachexia

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<th>Reduced food intake</th>
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<td>Anorexia</td>
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<td>Nausea, vomiting</td>
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<td>Altered taste and smell</td>
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<th>Local effects of tumor</th>
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<td>Odynophagia, dysphagia</td>
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<td>Early satiety</td>
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<td>Intestinal or gastric outlet obstruction</td>
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<td>Malabsorption</td>
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<th>Effects of cancer treatment</th>
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<td>Surgery</td>
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<td>Altered mastication, swallowing</td>
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<td>Postgastrectomy syndromes</td>
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<td>Pancreatic insufficiency</td>
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<td>Anastomotic stricture</td>
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<td>Chemotherapy</td>
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<td>Nausea, vomiting</td>
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<td>Altered taste and smell</td>
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<td>Stomatitis, mucositis</td>
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<td>Diarrhea</td>
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<tr>
<td>Radiation therapy</td>
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<tr>
<td>Anorexia, nausea, vomiting</td>
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<td>Altered taste and smell</td>
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<tr>
<td>Xerostomia, mucositis</td>
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<tr>
<td>Gastrointestinal mucosal damage</td>
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<td>Late strictures</td>
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<td>Psychosocial</td>
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<td>Depression</td>
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<td>Anxiety</td>
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<td>Learned food aversion</td>
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setting of semistarvation, such as a reduction in REE. On the contrary, the tumor-bearing host reacts without decreasing REE and with important alterations in carbohydrate, fat and protein metabolism [1]. Glucose production and utilization are altered, insulin resistance often occurs and there is equal mobilization of fat and skeletal proteins without sparing of the muscle protein. This energetic and metabolic impairment contributes to protein breakdown and tissue wasting and to some extent likens the metabolic response of the tumor-bearing host to the stress and sepsis responses. It has been hypothesized that some of the calories and proteins wasted by the host may be used by the tumor itself for its metabolism and growth.

The association between cancer malnutrition and poor outcome has been known for many years [2]. There is evidence that nutritional depletion causes alterations in both cellular and humoral immune function and inflammatory
responses, making patients more susceptible to poor wound healing, increased infectious complications, prolonged postoperative ileus and longer hospital stay.

To date, it has been proven that repletion can ameliorate several host-defense mechanisms, but only for severely malnourished cancer patients undergoing surgery has the use of nutritional support been shown to reduce morbidity and mortality after operation [3–5].

Therefore, a nutritional evaluation of the cancer patient has to be done at the time of diagnosis in order to detect specific nutrient deficits and to identify severely malnourished patients who are at high risk for increased morbidity and mortality and may benefit from nutritional support.

**Nutritional Assessment**

Nutritional status can be established by using different clinical, anthropometric and laboratory parameters to determine whether a given patient is either well-nourished or malnourished [5].

**Clinical Parameters**

A complete history and a thorough physical examination by an experienced physician represents a simple and reliable method for determining the nutritional status and it is usually enough to define the presence of severe depletion.

Malnutrition may be classified as mild (WL <10%), moderate (WL between 10 and 20%), or severe (WL >20%). A recent (within 6 months) loss of 10% or more of the usual body weight is indicative of significant malnutrition and of increased risk of morbidity and mortality. Patients should also be asked about recent dietary changes, onset of anorexia, food aversions or altered taste and bowel habits. The patient should be questioned regarding the presence of gastrointestinal symptoms such as nausea, early satiety, vomiting, abdominal pain and diarrhea. Previous gastrointestinal or pancreatic resections and underlying chronic diseases may affect both food intake and absorption.

Depletion in the tumor-bearing host usually stems from a combination of marasmus (reduced intake of both protein and calories) and kwashiorkor (protein deficiency with an adequate calorie intake). Patients affected mostly by marasmus may present decreased subcutaneous fat, as suggested by redundant skinfolds and diminished lean muscle mass, while those suffering mostly from kwashiorkor may also have anasarca, ascites and hepatomegaly.

**Anthropometrics**

Anthropometric measurements are useful in estimating body fat and lean muscle composition based on the patient’s body weight, height, skinfold thickness and upper arm circumference. Values are compared to a standard, based on age- and sex-matched population controls. However, unless a patient is significantly mal-
nourished, anthropometrics may be helpful only after serial evaluations to monitor change.

Skin testing for delayed cutaneous hypersensitivity (DCH) is performed to evaluate the immune function by intradermal injection of several antigens including purified protein derived of tuberculin, mumps, trichophyton and *Candida*. Yet, anergy to skin testing becomes evident usually only when WL exceeds 10% and can also be induced by many other factors.

**Laboratory Tests**

The degree of visceral protein depletion can be estimated by determining serum levels of albumin (Alb), transferrin (TFN), prealbumin and retinol-binding protein. The concentration of these proteins reflects the patient’s nutritional status but might also be affected by changes in salt and water balance.

The normal concentration of serum Alb ranges between 3.5 and 5.0 g/dl. Levels below 3 g/dl are associated with higher morbidity and mortality and represent a marker of severe depletion. Further, in determining the nutritional status and in monitoring the effects of nutritional support one has to consider the half-life of these proteins.

In an attempt to find a single method to quantify the extent of malnutrition and to correlate it to the risk of complications, the Prognostic Nutritional Index (PNI) has been proposed. This is a scoring system based on the triceps skinfold (TSF), serum Alb and TFN levels, and DCH and can be calculated as follows:

\[
PNI(\%) = 158 - 16.6 \times (Alb) - 0.78 \times (TSF) - 0.20 \times (TFN) - 5.8 \times (DHC),
\]

where Alb is in g/dl, TSF is in mm, TFN is in mg/dl and DHC is scored as 0 = negative, 1 = <5 mm reactivity, 2 = >5 mm activity.

**Nutritional Support**

Based on the currently available literature, several societies of parenteral and enteral nutrition have established indications and guidelines for the correct prescription of perioperative nutritional support in surgical patients [6–8]. These guidelines may be summarized in a decision-making flowchart (Fig. 1).

Once the need of nutritional support is established, the surgeon has to answer these 3 questions:

1. Which route is preferable for this patient?
2. What are the patient’s nutritional requirements?
3. What is the optimal composition of the nutritional support?
Fig. 1. Indications for nutritional support in patients undergoing surgery.

Choice of Nutritional Route
As a general rule, nutritional support should be provided via the enteral route whenever possible, because enteral feeding has less complications, is easier to administer, less expensive and more physiological than total parenteral nutrition (TPN). In fact, enteral feeding prevents some of the alterations related to the lack of use of the gastrointestinal tract during parenteral feeding, like atrophy of the
villi with the subsequent loss of the gut barrier and the possible development of bacterial translocation. Several clinical trials strongly suggested that early enteral feeding rather than TPN in traumatized and elective surgical patients may improve outcome [9]. Therefore, a patient should be put on TPN only when enteral feeding is contraindicated. The following are the current indications for TPN in a cancer patient: (1) malabsorption or severe diarrhea; (2) intestinal mechanical obstruction; (3) high output intestinal fistula (> 500 ml/day), and (4) short bowel syndrome (when enteral nutrition is ineffective).

Parenteral nutrition is usually started by administering 1,000 ml of the hypertonic solution over 24 h. Once the patient can metabolize dextrose and amino acids in 1,000 ml of the hypertonic solution during a 24-hour period, the flow rate can be increased to reach, within 2 or 3 days, the established caloric and protein requirement.

The best way to provide short-term enteral feeding is a nasoenteral tube. Small-bore (8–10 french) flexible tubes have reduced patient discomfort caused by larger-bore tubes. Gastric feeding is generally well tolerated because of the distensibility and the dilutional function of the stomach, as well as pyloric regulation of emptying into the duodenum. However, gastric feeding has a higher risk of aspiration than jejunal feeding. Thus, patients with severe gastroesophageal reflux, absent gag reflex, swelling disorders or altered mental status are not candidates for gastric feeding. For such patients, nutritional therapy should be provided via a nasojejunal route after the correct positioning of the catheter tip has been documented by X-ray.

The enteral solutions used should be nutritionally adequate, well tolerated, easy to prepare and economical. Four types of enteral formulas are available: blenderized formulas; nutritionally complete commercial formulas, chemically defined liquid diets, and modular formulas.

Blenderized tube feedings may be composed of any food that can be blenderized. The caloric concentration varies from 0.6 to 1.3 kcal/ml. These formulas are the less expensive but require a long time for preparation and a large-bore tube (14 french) for infusion due to viscosity.

Nutritionally complete formulas are the regimen of choice because of the relatively low cost, easy preparation and adequacy of nutrients. These are polymeric formulas with intact proteins. Most are isotonic with a caloric density of 1 kcal/ml but are also available as high-calorie, high-nitrogen, hyperosmolar formulas that provide 1.5–2 kcal/ml. Continuous pump infusion is recommended for delivery into the stomach or jejunum to avoid gastrointestinal complications.

Chemically defined or elemental formulas contain hydrolyzed proteins and crystalline amino acids and are more promptly absorbed. Elemental diets are indicated in patients with special requirements as a consequence of deficits in absorption, e.g. patients with severe radiation enteritis, intestinal fistulae, short bowel syndrome, etc.
Table 2. Harris-Benedict equation and correction factors for determination of energy requirements

<table>
<thead>
<tr>
<th>Condition or level of activity</th>
<th>Correction factor</th>
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<tr>
<td>Confined to bed</td>
<td>1.2</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>1.2</td>
</tr>
<tr>
<td>Fever</td>
<td>1.0 + 0.13 per °C</td>
</tr>
<tr>
<td>Severe trauma</td>
<td>1.2–1.4</td>
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<tr>
<td>Sepsis</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>Necrotizing pancreatitis</td>
<td>1.2–1.5</td>
</tr>
<tr>
<td>Major burns</td>
<td>1.5–1.8</td>
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<tr>
<td>Starvation</td>
<td>0.7</td>
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Basal energy expenditure (BEE) for women (kcal/day): BEE = 655 + [9.6 × weight (kg)] + [1.7 × height (cm)] – [4.7 × age (years)].

BEE for men (kcal/day): BEE = 66 + [13.7 × weight (kg)] + [5.0 × height (cm)] – [6.8 × age (years)].

Resting energy expenditure (REE) = BEE × correction factor.

Modular formulas consist of core modules of protein or carbohydrate or fats. Modules of vitamins or minerals are also available. This type of enteral nutrition can be used as supplements in combination with other enteral formulas or combined in different ways to meet special requirements.

Except for blenderized formulas, all enteral feeding should be delivered by continuous gravity or better by pump-controlled infusion. After tube placement, infusion is begun with a 5% dextrose solution at 20–30 ml/h for the first 12–24 h. Then, it is switched to full-strength formula at the same rate. The rate of infusion can be increased by 20–30 ml every 24 h as tolerated by the patient up to reaching the nutritional goal.

Daily Requirements

Whatever route or regimen has been selected, the daily requirements for calories, proteins, fluids, electrolytes, vitamins and trace elements should be satisfied.

An accurate measurement of the REE is obtained by indirect calorimetry that determines gas exchanges in a thermoneutral environment. Yet, the high costs of the method prohibit routine use outside the research setting. Caloric requirements can also be calculated based on sex, age, weight and height using the Harris-Benedict formula. The basal energy expenditure is then adjusted by a correction factor related to the level of activity and the clinical conditions of the patient. Practically, the caloric requirement of surgical patients never exceeds 25–28 kcal/kg/day with the exception of subjects suffering from large burns, acute necrotizing pancreatitis, major trauma, or severe sepsis (Table 2).
Nonprotein calories are supplied as a combination of carbohydrates and fat, usually 70% for carbohydrates and 30% for lipids. The maximal rate of glucose oxidation in the adult is 7 g/kg/day. Patients with high-caloric requirements or severe glucose intolerance should be given calories in excess as lipid.

The average protein requirement in normal subjects is 0.8 g/kg/day for maintenance and is 1.2–1.5 g/kg/day for anabolism. Hospitalized cancer patients have increased requirements and should be provided with 1.5–2.0 g/kg/day. Dietary nitrogen should be supplied with a calorie-to-nitrogen ratio ranging from 125 to 150 cal/g nitrogen (1 g nitrogen = 6.25 g protein). A 24-hour urine collection for urinary urea nitrogen can be performed to calculate the nitrogen balance for a more precise protein delivery.

In addition to calories and protein, electrolytes, vitamins and trace elements are required nutrients. Ongoing urinary and gastrointestinal losses of fluid and electrolytes must be considered and specific electrolyte, vitamin or mineral deficiencies identified and corrected. Required daily vitamins and minerals are included in most enteral formulas or can be provided as multivitamin and trace element parenteral preparations.

**Composition of Nutritional Support**

In cancer surgical patients, impairment of immune system is multifactorial, as a consequence of the tumor itself, the cancer cachexia, the reduced food intake, the surgical injury and the effect of multimodality treatment. Therefore, it is not surprising that, in these patients, standard nutritional support alone may fail to restore the normal immune competence. Hence, in the last 10 years, the interest of several authors moved from the simple calculation of caloric and nitrogen requirements to the study of new and specific dietary substrates (pharmaconutrients) with the ability to modulate host-defense mechanisms, inflammatory responses, intestinal barrier function, tissue oxygen, nitrogen metabolism, ischemia/reperfusion injury, etc., which could represent theoretical mechanisms for better clinical outcome. Among the most carefully investigated immunonutrients are:

1. Arginine which improves macrophage and natural killer tumor cytotoxicity, bactericidal activity, and vasodilatation through production of nitric oxide, stimulates T-cell proliferation and activation, and modulates nitrogen balance/protein synthesis and cytokine production [10]
2. ω-3 polyunsaturated fatty acids, derived from fish oil, are potent anti-inflammatory agents through the modulation of eicosanoid synthesis. They regulate the fluidity of cell membranes, intervene in the pathway of coagulation, and upregulate the immune response [11]
3. Glutamine is known to facilitate the transport of nitrogen between organs, to reduce the skeleton and intestinal protein waste during stress conditions, to enhance the macrophage and neutrophil phagocytosis and lymphocyte function, and to preserve the intestinal permeability and function, by being the major fuel for different cell types [12]
These immunonutrients, tested separately or in various combinations in different experimental settings, have been proven to significantly reduce septic morbidity and mortality.

**Glutamine Supplementation**

Several clinical studies showing the outstanding metabolic advantages of glutamine (Gln) supplementation have been reported and recently reviewed by Hall et al. [12]. Briefly, these trials demonstrated that Gln administration improves nitrogen balance and increases plasma and muscle Gln concentration, stimulates protein synthesis, reduces protein breakdown, increases cell proliferation and function, enhances D-xylose absorption and improves other parameters of intestinal function. In contrast, few studies about Gln provision and clinical outcome in humans have been published: Ziegler et al. [13] first demonstrated in humans that Gln-supplemented feeding improves the clinical course of patients with hematological tumors undergoing allogeneic bone marrow transplantation. Patients receiving Gln had a significantly lower incidence of positive microbial culture and clinical infection. Hospital stay was significantly shortened in treated patients compared to controls.

In a recent paper, Morlion et al. [14] randomized 28 patients having elective surgery for colorectal malignancies. Patients receiving postoperative parenteral alanine-Gln dipeptide revealed improved nitrogen balance, improved lymphocyte recovery on postoperative day 6 and increased generation of cysteine-leukotrienes from granulocytes. Postoperative hospital stay was 6.2 days shorter in the Gln-supplemented group. The authors did not report the infectious complication rate, and mean length of stay in the control group was 21.7 days, which is considerably higher than the average for this type of surgery. In intensive care unit patients Gln supplementation has been reported to improve survival [15, 16].

Thus, a rational base exists for clinical use of supplemental Gln in catabolic, critical or depleted patients, but to date clinical studies suggesting beneficial effects on outcome have to be confirmed by further trials, particularly in cancer surgical patients.

**Postoperative Multiple Component Formulas**

In several clinical prospective randomized trials [17–22] the administration of diets supplemented with different combinations of immunonutrients showed, with surprising consistency, a significant improvement in the host-defense mechanisms and modulation of the inflammatory response. Moreover, the treated patients more rapidly overcome the postsurgical immune depression than subjects receiving standard diets. However, this enhancement occurred with some delay usually after 5–8 postoperative days. In fact, in the first days after surgery a similar impairment of phagocytosis ability, delayed hypersensitivity response to skin tests, alteration of cytokine profiles, reduction of immunoglobulin levels, number of activated T and B cells and lymphocyte mitogenesis was found by
comparing patients fed with supplemented or standard diets. The delayed recovery in immune response and metabolic parameters might explain why supplemented diets, given exclusively in the postoperative course, led to variable improvements in outcome.

In fact, many prospective randomized studies were performed with the declared primary endpoint to investigate the potential advantages of immunonutrition on clinical course. Some authors reported a significant decrease in postoperative or postinjury complications, others did not confirm these results [23]. Nevertheless, two recent meta-analyses suggested that enteral immunonutrition given after surgery or trauma significantly reduced the rate of infection and the length of hospitalization [24, 25].

A different approach to overcome the intrinsic limitation of early postoperative enteral feeding may be to anticipate the administration these immunoenhancing diets before operation (when possible) to obtain efficacious concentrations of immunonutrients at the time of surgical injury.

**Perioperative Immunonutrition**

In humans undergoing major operation for neoplasm, the provision of immunonutrients before surgery affected the ratio of generated leukotriene B4/B5 from peripheral neutrophils [26]. In an additional trial supplemented diets were administered perioperatively to patients with gastrointestinal cancer who were candidates for major surgery [27]. Before operation patients were randomized to drink 1 liter/day, for 7 consecutive days, of a supplemented liquid diet or a isonitrogenous, isocaloric control formula. Postoperative enteral feeding with either the supplemented or control diet was started 6 h after surgery with a jejunal infusion and increased to reach the full nutritional regimen (25 kcal/kg). Perioperative supplementation with immunonutrients prevented the early postoperative depression of both polymorphonuclear cells and lymphocyte function and their circulating levels.

The patients fed the supplemented diet had a higher CD4/CD8 ratio than the control group. The prompt and effective immune response observed in the supplemented group immediately after operation might be due to adequate plasma and tissue concentrations of immunonutrients already available at the time of surgical stress. Moreover, in patients receiving the supplemented formula the postoperative increase in IL-6 was significantly lower than in the control group. This was paralleled by the postoperative variations of C-reactive protein, whereas the synthesis of prealbumin and retinol binding protein after operation was significantly improved in the supplemented group. At the beginning of surgery, intraoperative gut microperfusion (measured by laser Doppler flowmetry technique) was significantly higher in the patients receiving the supplemented diet than in the control patients. Furthermore, in the control group there was a marked reduction in microperfusion at the end of surgery. The higher values of intramucosal jejunal pH (measured by intestinal tonometry) observed in the supplemented
group suggested that an adequate splanchnic blood flow promotes a good tissue oxygen tension, delivery and utilization. In a subsequent phase III prospective, randomized double-blind trial [28], with 206 cancer patients, it was shown that perioperative immunonutrition significantly decreased the rate of postoperative infections, the use of antibiotics, and allowed a 2-day-shorter length of hospital stay. Moreover, this approach led to a significant saving of health resources used to treat postoperative complications [29].
Multimodality Treatment

Current concepts on cancer therapy are frequently based on multimodality treatment with patients undergoing surgery plus radio- and chemotherapy given pre-, intra- or postoperatively. It is well known that these therapies, especially when provided in an aggressive fashion, may induce damage to both the immune system and the gastrointestinal tract, sometimes resulting in a decrease in food intake and a subsequent worsening of the nutritional status.

Patients submitted to major gastrointestinal surgery, undergoing adjuvant radiation therapy and chemotherapy, could benefit from prolonged nutritional support via a feeding tube during adjuvant treatment. Daly et al. [22], in a randomized controlled study, reported an increased requirement for hospitalization in patients given oral feeding alone vs. patients who received supplemental enteral feeding, and a 61% cross-over rate to the tube-feeding regimen because of the onset of diarrhea, dehydration, inanition or other complications during radiation or chemotherapy.

The correct management of patients undergoing multimodality treatment is still controversial. As a general recommendation, patients should be carefully monitored for their nutritional status and calorie intake before, during and after multimodality treatment (Fig. 2).

References


Discussion

Dr. Baracos: Do you believe that the fixed recipe for the immunonutrients in the supplement you described was optimal for the patient group you are treating?

Dr. Gianotti: I've no data to show that, but this diet was on the market, so from a pragmatic point of view we wanted to test whether it offered any advantages for the patients when compared with a control diet. It may not be a perfect mixture of immunonutrients but it certainly works, because you can decrease the rate of infection by 40–50%, with substantial savings in health care resources.
Dr. Asprer: The question I'd like to ask is regarding the beneficial effects seen after early enteral immunonutrition. I'm curious about whether the beneficial effect is simply due to early stimulation of the gut, which activates gut-associated lymphoid tissue (GALT), or whether the effect is in fact due to the immunonutrients that you supply. I think this might be a little difficult to show. If you're unable to achieve the dose required until the 4th day, doesn't that imply that the immune benefit is probably due to the stimulation of the GALT?

Dr. Gianotti: If the effect was due to stimulation of the GALT, or to a reduction of bacterial translocation, or to an increase in trophic hormones, we should have seen a positive result in our trial of standard enteral versus parenteral feeding, but we didn't see that. However, we saw a trend towards a better outcome using only postoperative feeding in the immunonutrition group. I'm sure the issue of timing and dosage in the postoperative period is crucial: you can start infusing enteral feeding on the day of surgery, but this does not allow you to reach full intake for at least 3 or 4 days, whatever kind of strategy you use. I guess this is the intrinsic limitation of the postoperative approach.

Dr. Asprer: The postoperative dosing problem can be solved by combining an early slow enteral drip with simultaneous parenteral nutrition. In the last study that you presented, the preoperative feeding regimen that you gave had the same beneficial effect as the perioperative regimen. In emergency cases, in patients where that is not possible, do you think the perioperative immunonutrition that you described would have the same level of beneficial effect?

Dr. Gianotti: In emergency cases, a preoperative regimen is, of course, not applicable. However, in ICU patients the beneficial effect of postoperative infusions has been shown in two meta-analyses [1].

Dr. Nitenberg: There is a good study comparing the administration of saline in the postoperative period with immunonutrition, which showed no benefit of immunonutrition [2]. Don't you think that rings the death knell for parenteral or enteral nutrition in the postoperative period except in high-risk or malnourished patients?

Dr. Gianotti: That trial was a good one, but on the other hand the maximum energy intake was only around 30% of normal over a mean period of 1 week. If you only gave one third of the recommended dose of antibiotics in a trial you might not be surprised if you failed to get a positive result. Under such circumstances you can't really conclude that the regimen doesn't work—you have to be able to give adequate amounts of the substance you are testing, in a reliable way, before you can say that. However, my guess is that there is no place for total parenteral nutrition any more, except in the conditions that I cited.

Dr. Nitenberg: I don't totally agree, but we can discuss that later. But also, what about the recent work from McCarter on the preoperative administration of immunonutrition, and the poor results obtained. The study was not exactly comparable to yours, but they did not obtain any increase in plasma concentrations of arginine or glutamine, or modification of CD4 or CD18, and there was no reduction in the postoperative complication rate. Could you comment on the negative results of that study?

Dr. Gianotti: Well, I was lucky enough to talk to John Daly, the senior author of this trial. He explained the negative result on the basis that first there were very small numbers of patients, only 12 in each group, which doesn’t make much sense, and second that the diet, which was given at home unsupervised, tasted so bad that the patients could not consume the required amount.

Dr. Waitzberg: I understood you to say that the last study you described was done in well-nourished patients. Is that true?

Dr. Gianotti: Yes.

Dr. Waitzberg: It’s intriguing that preoperative forced enteral feeding in well-nourished patients decreases infection. Are you proposing a new concept, that well-nourished patients should receive forced enteral preoperative feeding? In that case, what variables ought to be
measured in such patients, and do you think you are changing immune function rather than nutrition?

**Dr. Gianotti:** You’ve hit the nail on the head. The real point is that well-nourished patients undergoing major surgery experience immune-suppressive effects in the same way as malnourished patients. Everybody knows that if you operate on well-nourished patients, you have fewer infections and fewer complications than you do in malnourished patients, but you still have complications. You cannot hide the fact that the complication rate after major surgery for esophageal or pancreatic cancer is about 30% and this goes up to 50% in malnourished patients. This is not primarily a matter of nutrition, it is a matter of manipulating the immune response by nutrients that happen to have the capacity to do this. We are moving away from a purely nutritional concept towards a ‘pharmacological’ effect of nutrients, which is very different from giving nitrogen, energy and so on. I don’t at present know of any variables that you can measure to assess which patients will benefit.

**Dr. Bloch:** As a nutritionist, I’d like to commend you as a surgeon for your efforts in running these prospective clinical trials. We attempted to do a study on gastrointestinal patients in our center, but we ran into a logistical problem. We found that the surgeons wanted to remove the decompression tube at around 3–4 days after the operation, after which our patients couldn’t tolerate the feeding, so we were never able to advance them to an adequate regimen. Can you comment on that problem?

**Dr. Gianotti:** Did you feed into the stomach or into the small bowel?

**Dr. Bloch:** In the jejunum.

**Dr. Gianotti:** That’s not been my experience. We don’t use decompression tubes for gastric or esophageal surgery. We perform a feeding jejunostomy at the end of the operation on the second intestinal loop. At 6–12 h after surgery, there is usually some bloating and cramps, but most patients recover from this side effect of early enteral feeding after about 12 h. And you can control cramps with pain-relieving drugs, which are very effective. You may be scared about bloating, but when you’ve had a little experience you realize nothing happens.

**Dr. Bachmann:** Have you any idea of what the energy intake was in the patients in your control group in the 5 days before surgery?

**Dr. Gianotti:** Not a very precise measurement but these patients were consuming about 1,500 kcal/day as normal food.

**Dr. Nitenberg:** Do we need to have a mixture of immunonutrients to improve the immune status of patients? When you look at the different immunonutrients used in different commercial formulas, they are slightly different in proportion and quality. Why? There is at least one study showing an excellent effect with glutamine alone. Don’t you think it’s time to go back to the bench and determine the exact value of each immunonutrient? And don’t you think it’s time to see if anything is to be gained by adding several immunonutrients in one mixture?

**Dr. Gianotti:** Of course I agree with you. From a theoretical point of view, it was stupid to formulate enteral diets containing all these agents without really knowing which ones worked. But from a practical point of view, this formula works: it reduces complications for your patients, it reduces costs, and it reduces length of stay, so why should we go back and test whether it is arginine that is working, or RNA, or glutamine, or whatever. What is the point?

**Dr. Nitenberg:** The point is, I need to know how it works. Maybe it could be important for the future.

**Dr. Gianotti:** Well, we know that it works. Maybe in the future we will know how. So far we know that it works. For me that is enough.

**Dr. Arnaud-Battandier:** Did you have an opportunity to look at the intestinal mucosa at the time of surgery to check the immune compartment?
Dr. Gianotti: That’s a very good point. We didn’t, but that would be a very interesting thing to do, to take out a piece of gut and analyze the immunonutrient content. Thank you. What we did was to measure the intestinal oxygen tension by micropolarographic probes and measure intestinal oxygen metabolism by tonometry. Both were increased in the immunonutrient group.

Dr. Meier: We have done a small study on 6 patients fed by percutaneous endoscopic gastrostomy (PEG), with duodenal biopsies before and after PEG feeding. We measured RNA, DNA, and protein content in the biopsies and found an increase in all three during 3 months of treatment with an immunonutrition solution. It was only 6 patients, but you can see something in the mucosa.

Dr. Arnaud-Battandier: Did you look at the enteral side or GALT? Did you look at the lymphocyte compartment?

Dr. Meier: No, it was in the whole biopsy.

Dr. Pichard: Regarding the 240 patients in the last study you presented to us, I expected you to have at least a few patients with major complications who have to go to the intensive care unit (ICU), for example, for aspiration, pneumonia, fistula, and so on, so I’m a little surprised about your cost analysis. How is it possible to have complications that cost so little? We all know that pneumonia or a few days in the ICU cost at least 10,000 dollars, so how could you have complications that cost as little as 1,000 or 2,000 dollars? It seems too cheap.

Dr. Gianotti: You are right. We had complications like peritonitis, pneumonia, and septic shock which cost 20,000 dollars. What you saw was the mean of all the complications per patient. So the mean complication cost was about 6,000 or 7,000 euros. Of course we also had complications that were of very low cost, such as urinary tract infections or small wound infections.

Dr. Pichard: But I think you would agree that in most health-providing systems, most money is used to treat major problems. So even if your results are quite convincing in terms of the majority of the patients, I’m not sure that they are still valid if you look at the most difficult problem patients.

Dr. Gianotti: We can do that because we have all the data. That’s a very good suggestion. We will go back and look at the major complications.

References
