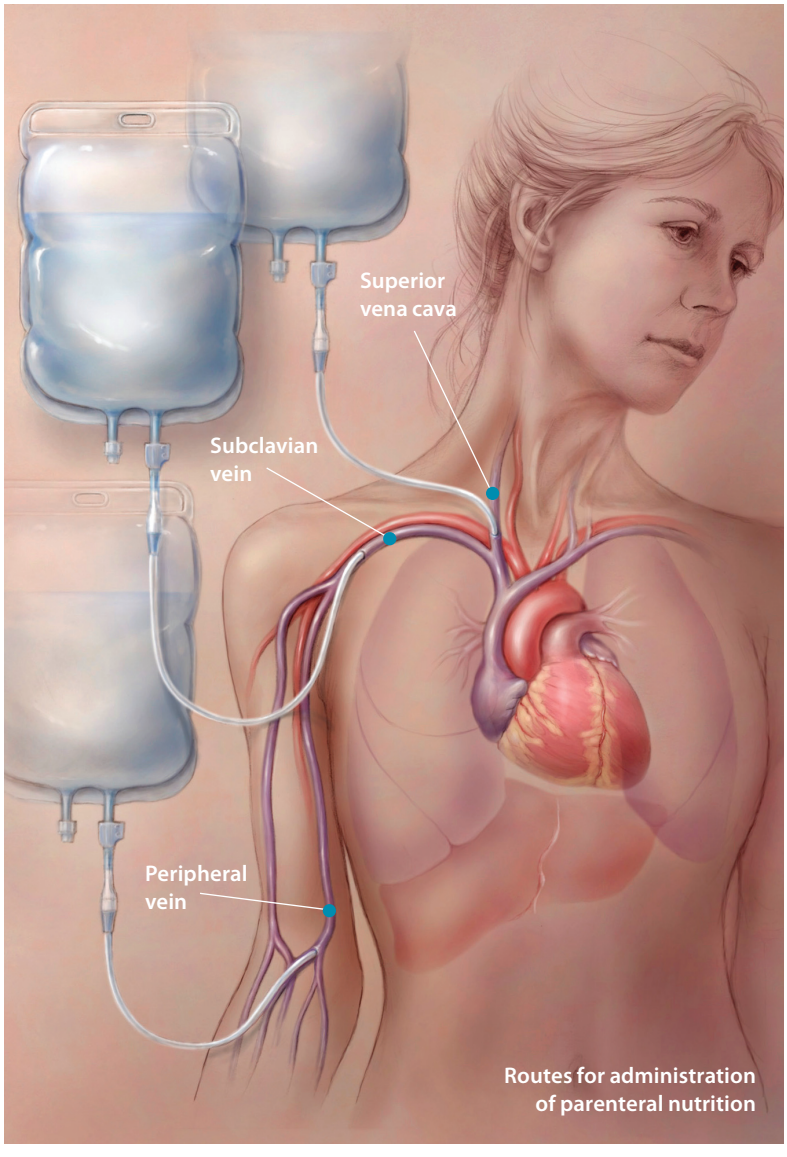
Benefits and risks of parenteral nutrition in patients with cancer

Nutritional status can have a significant impact on patients with cancer, and PN may help some patients respond better to treatment.



Routes for administration of parenteral nutrition

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The medical community has been interested in intravenously administered nutrition since the 1600s; however, reliable sources of IV nutrients were not established until the 1960s. As a young intern, Stanley Dudrick, MD, struggling to save patients who could not be nourished orally or via tube feeding, dedicated himself to finding a way to supply nutrients to patients lacking a functional GI tract.[1] He was able to demonstrate that IV nutrition could support growth and development in beagle puppies. Continuing to refine his nutrient solution, he began administering his nutrient solution intravenously to select human patients.[1]

Another challenge was finding adequate venous access for administration of the hypertonic nutrition. Dudrick found that using subclavian vein cauterization allowed nutrients to be quickly diluted within the central venous system, thereby decreasing the likelihood of thrombotic complications. In 1968, Dudrick discharged a 36-year-old patient with a nonfunctioning GI tract to home with his newly developed IV nutrition support. The patient had metastatic end-stage ovarian cancer; however, she was likely to die sooner from starvation than disease progression. The home nutrition support extended her life expectancy and improved her quality of life.

The development of parenteral nutrition (PN) contraindicated a long-held belief that nutritional administration entirely through the veins was impossible, impractical, or unaffordable. The

ability to supply nutrients to patients lacking a functional GI tract ultimately saved lives that would have otherwise been lost to malnutrition.

Early PN formulas consisted of dextrose and protein hydrolysates of either casein or fibrin, which were later replaced with crystalline amino acids. Intravenous lipid infusions were not available until the 1970s. In the 1980s, IV lipid emulsions became a source of calories. At the same time, the FDA approved total parenteral nutrition (TPN), nutrient admixtures of fat emulsions combined with other nutrients in one mixture. Today, PN is a complex mixture of up to 40 different chemicals or nutrient components. As with any complex formulation, stability and compatibility problems can occur. Improper compounding or contamination can result in harm or even death. Complications of PN include venous catheter infections, hepatobiliary disease, and glucose disorders. Complications can be minimized through careful patient selection. This article addresses the nutritional merits of PN and its use in oncology.

ENTERAL VS PARENTERAL NUTRITION

Specialized nutrition support (SNS) is available in two forms: parenteral nutrition and enteral nutrition. Both forms are used to prevent malnutrition in patients otherwise unable to satisfy estimated nutritional requirements via the oral route.

Patients at risk for malnutrition who are candidates for SNS experience an involuntary weight loss of more than 10% over a 2- to 3-month period, weigh less than 75% of his or her ideal or usual weight, and laboratory test results indicate prealbumin of less than 10 mg/dL, or have a history of inadequate oral intake for more than 7 days.

Enteral nutrition provides requisite nutrients to patients who have a functioning GI tract but cannot ingest nutrients orally. Enteral nutrition requires inserting a feeding tube directly to the GI tract to provide liquid nutrition via pump, bolus, or gravity feeding. It is recommended for patients in whom access to the GI tract does not cause trauma.

Parenteral nutrition provides requisite nutrients to patients intravenously, thereby bypassing a nonfunctional GI tract. The PN formulation provides energy, fluid, and various medications via peripheral or central venous access. PN is recommended for patients who may become or are malnourished and are not candidates for enteral nutrition. Parenteral nutrition should not be used routinely in patients with an intact GI tract. PN is associated with more infectious complications, does not preserve GI tract function, and is more expensive than enteral nutrition.

TABLE 1. Indications for parenteral nutrition

Bone marrow transplant patients with nausea, vomiting, and severe mucositis lasting for >5 d
Diarrhea with stool output >1 L/d
Failed enteral trials with postpyloric tube placement
High-output fistula
Intestinal hemorrhage
Intractable vomiting
Mesenteric ischemia
Paralytic ileus
Perioperative nutrition in critically ill patients
Peritonitis
Severe pancreatitis
Short bowel syndrome with <150 cm bowel
Small bowel obstruction

INDICATIONS FOR PARENTERAL NUTRITION

American Society of Parenteral and Enteral Nutrition (ASPEN) guidelines suggest that patients who cannot, should not, or will not eat enough to maintain adequate nutritional status and have the potential to become malnourished are appropriate candidates for PN.[2] These patients have failed enteral nutrition trials with postpyloric tube placement. PN is also indicated for patients with short bowel syndrome, particularly if less than 150 cm of small bowel remains after surgery and GI fistula except when enteral access can be placed distal to the fistula or volume output is less than 200 mL/day. Critically ill patients who cannot receive enteral nutrition and nothing-by-mouth status will last for more than 4 to 5 days are candidates for PN. It is also initiated in cancer patients with treatment-related symptoms that affect oral intake (eg, mucositis, stomatitis, esophagitis) if the symptoms last for more than 7 days (**Table 1**). Parenteral nutrition is not well-tolerated in cases of severe hyperglycemia, azotemia, encephalopathy, hyperosmolarity, and severe electrolyte and fluid imbalance, and it should be withheld until improvement is observed.

MACRONUTRIENT COMPOSITION

Carbohydrates are the primary source of energy for the human body. The brain and neural tissues, erythrocytes, leukocytes, the lens of the eyes, and the renal medulla either require glucose or use it preferentially. The base of all PN solutions is carbohydrates, most commonly dextrose monohydrate. Dextrose provides 3.4 kcal/kg and is available in

concentrations from 5% to 70%, with higher concentrations used primarily for patients on fluid restrictions.

Protein is necessary to maintain cell structure, tissue repair, immune defense, and skeletal muscle mass. Protein is provided in the form of crystalline amino acids in concentration ranging from 3% to 20%. Amino acids provide 4 kcal/kg.

Amino acid solutions are usually a physiologic mixture of both essential and nonessential amino acids. Disease-specific amino acid solutions are available and are primarily used for renal and hepatic disease. Patients with declining kidney function who are not yet candidates for dialysis are at risk for urea nitrogen accumulation when infused with nonessential amino acids. These patients receive only essential amino acids. Patients with severe hepatic encephalopathy may benefit from branch-chain amino acids (BCAAs).

TPN offers greater choices in formula selection, but is associated with increased risk of catheter-related bloodstream infections.

BCAAs are oxidized primarily in the muscle, rather than the liver, preserving hepatic metabolic pathways in case of liver failure. In general, disease-specific amino acid solutions offer an incomplete amino acid profile and should not be used for more than 2 weeks.

Lipids in oil-in-water emulsion concentrations ranging from 10% to 30% provide fats in PN. Lipid solutions currently available in the United States contain long-chain triglycerides (LCT) in the form of soybean or safflower oil, egg phospholipids as an emulsifier, water, and glycerol to create an isotonic solution.

Inclusion of lipids in IV nutrition prevents essential fatty acid (EFA) deficiency. Solutions that provide up to 4% of total calories from linoleic acid or 10% of total calories from safflower oil-based emulsions will meet daily EFA requirements. Patients who receive PN without lipids, usually those with an egg allergy, should be monitored for EFA deficiency. Excessive hair loss, poor wound healing, dry and scaly skin, and laboratory test results for a triene:tetraene ratio of more than 0.2 are indicators of EFA deficiency. In patients with egg phospholipid allergy, oil can be applied to the skin to prevent EFA deficiency. Recommended dosage is 2 to 3 mg/kg/d safflower seed oil for 12 weeks.

Lipids are useful for replacing excessive dextrose calories in cases of uncontrolled hyperglycemia or delayed weaning from mechanical ventilation due to hypercapnia. Lipids containing medium-chain triglycerides (MCT), fish oil, and olive oil have been available in Europe since 1984, but are just now available for research in the United States. Comparisons of the two emulsions indicate one MCT exerts less stress on the liver, improves plasma antioxidant capacity, reduces generation of proinflammatory cytokines, and improves oxygenation.

Essential vitamins and trace elements that are necessary for normal metabolism and cellular function are also added to PN solutions. The dosing requirements for vitamins and trace elements are generally higher than enteral requirements as patient needs are higher secondary to malnutrition.

PARENTERAL NUTRITION SOLUTIONS

PN solutions are classified as either total or peripheral based on route of administration and macronutrient composition. Total parenteral nutrition is delivered via a large-diameter central vein, usually the superior vena cava. Central access allows for the use of highly concentrated, hypertonic solutions and is preferred because the rate of blood flow rapidly dilutes the hypertonic feeding formulation to that of body fluids. Patients receiving PN for more than 2 weeks generally require central vein infusion via a temporary central venous catheter (CVC). Long-term usage requires a tunneled catheter, an implanted port, or a peripherally inserted central catheter (PICC). TPN offers greater choices in formula selection, but is associated with increased risk of catheter-related bloodstream infections. Specific conditions warrant caution when administering TPN (**Table 2**).

Peripheral parenteral nutrition (PPN) uses a peripheral vein for access rather than a central vein. Because it is administered into a peripheral vein, the osmolarity of PPN must be less concentrated than TPN and should not exceed 900 mOsm/L. Patients receiving PPN are at risk for vein damage and thrombophlebitis. PPN is not recommended

TABLE 2. Conditions that warrant caution with parenteral nutrition

Azotemia
Hyperglycemia
Hypernatremia
Hyperosmolarity
Hypochloric metabolic acidosis
Hypokalemia
Hypophosphatemia

for severely malnourished patients but rather for those with mild to moderate malnutrition who need repletion for not more than 2 weeks.

COMPLICATIONS

Metabolic The most common metabolic complications of PN are hyperglycemia and hypoglycemia. Limiting the amount of dextrose to less than 300 g/day can reduce the risk for hyperglycemia. Hypoglycemia is generally caused by sudden cessation of TPN solutions. To prevent hypoglycemia, PN should be decreased to half rate for 1 hour and then discontinued.

Increased caloric provisions from PN should help reverse the effects of malnutrition and promote better response to treatments.

Refeeding syndrome is a severe alteration of electrolyte balance caused by a rapid increase in nutrient intake in malnourished patients; it is a less common but more serious complication. Limiting the amount of calories, particularly dextrose to start, can reduce the risk of refeeding syndrome. Fluid status, potassium, phosphorus, and magnesium status need to be checked and corrected until stable at full PN rate. PN should be increased gradually over 2 to 3 days.

Other metabolic disturbances associated with long-term parenteral nutrition are metabolic bone disease such as osteomalica and osteoporosis. Hepatic disease, biliary disease, and renal disease (such as decreased glomerular filtration rate) have been noted in patients on long-term parenteral nutrition, as well as gastrointestinal disturbances, including gastroparesis.

Cholestasis, gallbladder stasis, and cholelithiasis are gallbladder-related potential complications of PN administration. Patients with short-bowel syndrome are particularly at risk for gallstone formation. If possible, a transition from parenteral to enteral nutrition can stimulate the gallbladder, which can help avoid gallbladder-related complications. Otherwise, the use of cyclic PN, carbohydrate restrictions, and avoidance of overfeeding will help minimize possible side effects.

Parenteral nutrition is associated with GI atrophy. The lack of enteral stimulation causes villus hypoplasia, colonic mucosal atrophy, decreased gastric function, impaired gastrointestinal immunity, bacterial overgrowth, and bacterial translocation. A reduction in mass of both the small and large intestine has been associated with PN. Reduced stimulation by gastric hormones and inadequate pancreatic and gallbladder secretions contribute to PN-associated gastrointestinal atrophy. Enteral feedings should be initiated if feasible. Beneficial effects have been seen in animal models with enteral administration in amounts as small as 10% to 25% of total caloric requirements.

PN provides postoperative nutrition support for patients who have had intestinal resections. These patients often receive long-term PN, particularly when less than 150 cm of small bowel is remaining after resection. This group of patients is prone to a high volume of acidic gastric secretions, depending on the length of bowel resected. Gastric hypersecretion can lead to peptic ulcers and hemorrhagic gastritis. Histamine, H2 receptor antagonists, cimetidine (Tagamet, generics), ranitidine (Zantac, generics), and famotidine (Pepcid, generics) are used to reduce gastric output and prevent ulcers after extensive small bowel resections. These medications can be added to the PN solution and administered over a 24-hour period.

Infectious The vascular access devices can be the source of infectious complications. These complications are typically associated with endogenous flora, contamination of the catheter hub, seeding of the device from a distant site, and contamination of the PN solution.

Mechanical Venous thrombosis is noted in patients receiving long-term PN. Catheter occlusion may also occur during long-term PN administration.

MALNUTRITION IN ONCOLOGY

Malnutrition is the most common secondary diagnosis in cancer patients. Even patients who are eating can become malnourished because of specific biochemical and metabolic changes associated with cancer. These metabolic changes impair nutritional status and contribute to cancer-related malnutrition, anorexia, and cachexia. At least 50% of cancer patients are cachetic.[3] Recent reviews indicate cachexia is even more widespread among patients with advanced cancer.[4]

Cachexia is derived from the Greek word meaning "bad condition," and is characterized by anorexia (loss of appetite), weight loss, muscle wasting, and chronic nausea. Other noted effects are changes in body composition, alterations in carbohydrate, protein, and lipid metabolism, and depression. Cancer-related metabolic changes lead to preferential depletion of lean body mass as a source of calories. In this way cachexia differs from simple starvation, where the body will metabolize fat stores and protect lean body mass.

Anorexia, the loss of appetite and food intake, is noted in 50% of newly diagnosed cancer patients. Early satiety, taste and smell alterations, food aversions, nausea, and vomiting are contributory factors to anorexia.

Cancer treatments such as chemotherapy and radiation treatment often cause nausea, vomiting, diarrhea, mucositis, and taste alterations (dysguesia). These treatment effects can lead to malabsorption. Cancer operations may result in decreased intake, particularly in the case of surgery to the mouth and neck, which may cause dysphagia. The GI tract can develop physical obstructions, which are often the result of tumor burden. GI obstructions result in decreased intake and are associated with emesis after oral intake. Finally, the depression that frequently accompanies the diagnosis of cancer leads to decreased intake. Eating, which is considered a pleasant experience for most, is no longer pleasant because of side effects, stress, and worry.

NUTRITIONAL ASSESSMENT

Malnutrition is associated with an increase in postoperative morbidity and mortality. A thorough clinical assessment and frequent reassessments are important steps to guarantee timely nutrition interventions. Various tools are available to assess nutritional risk.

The patient-generated subjective global assessment (PG-SGA) is a nutrition assessment tool designed to identify malnutrition in cancer patients.[5] Sections on short-term weight status, food intake changes, symptoms that impact nutrition intake, and functional capacity are completed by the patient. A three-part physical assessment that includes evaluation of metabolic demands, degree of metabolic stress, and evaluation of fat stores is completed by the clinical practitioner.

Body weight and weight loss are the most important anthropometric indicators of severity and progression of disease. Up to 45% of all cancer patients experience weight loss greater than 10% of usual body weight. There is a direct correlation between percentage of weight loss from usual body weight and complications or mortality. Weight loss is dependent upon fluids and hydration status. Edema and changes in intracellular fluid status are important factors to consider when assessing weight loss and protein calorie malnutrition.

Physical examinations evaluate for muscle wasting, edema, and ascites. Cachexia-related muscle wasting is often noted in the temporal area, arms, and legs. Muscle wasting occurs in obese patients; however, it may be more difficult to recognize.

Biochemical and laboratory tests including serum and urinary tests complete the nutrition assessment of the patient. Visceral protein is generally used to monitor protein status. Albumin, often used to monitor protein status, is considered a poor indicator of protein stores due to its long half-life (20 days). Albumin is also affected by hydration status. Prealbumin is considered a more reliable marker because its half-life is 2 to 3 days. Laboratory tests also identify micronutrient deficiencies.

TPN IN CANCER PATIENTS

Total parenteral nutrition is known to be effective in cases of malnutrition in patients who do not have cancer. However, TPN has not been shown to positively affect the nutritional status in patients with cancer.[2] This is due in part to the metabolic changes associated with cancer.

Malnutrition places patients with cancer at greater risk for complications associated with surgery, chemotherapy, and radiation therapy. Increased caloric provisions from PN should help reverse the effects of malnutrition and promote better response to treatments. PN has been shown to slow protein catabolism and reverse visceral protein loss at times; however, repletion has not effectively translated to clinical benefit.[6]

Chemotherapy is associated with a number of insults that impact nutrition status including nausea, vomiting, mucositis, gastrointestinal dysfunction, and learned food aversions.

Overall survival, disease-free survival, and time to relapse were improved in patients undergoing bone marrow transplantation who received TPN.

These symptoms cause further nutrition decline in already compromised patients and can lead to increased morbidity and mortality during treatment.

A review of trials of TPN and chemotherapy indicates little difference in clinical outcome and had little effect on maintaining body composition.[7,8] Weight gain associated with TPN therapy was due to the accumulation of body fat and not an increase in lean body mass.

TPN has been effective in bone marrow transplantation (BMT). BMT requires intensive chemotherapy, causing severe nutritional symptoms. Overall survival, disease-free survival, and time to relapse were improved in patients undergoing BMT who received TPN.[9,10]

Radiation therapy increases risk of malnutrition. The severity of weight loss and malnutrition depends on the

area undergoing radiation and dose, duration, and volume of therapy. Symptoms associated with radiation treatment include nausea, vomiting, mucositis, dysphagia, xerostomia, trismus, diarrhea, enteritis, and malabsorption. One study of radiation therapy and TPN supplementation did not indicate improved clinical response, decrease in therapy-related complications, or improved survival rate.[11]

PN IN PATIENTS WITH ADVANCED CANCER

The use of PN and home PN in patients with advanced cancer remains controversial. The ASPEN guidelines state: "The palliative use of nutrition support in cancer patients is rarely indicated."[12] However, for patients with cancer and their families, severe anorexia and resultant weight loss produce great anxiety and stress. Parenteral nutrition, home PN in particular, can provide some sense of relief that the patient is receiving some nutrition. It cannot reverse cancer-related cachexia because cachexia is mediated by chronic disease inflammatory factors. A recent study revealed that home PN adminstration seems to relieve anxiety because patients are receiving attention from health care aides.[13] PN serves as a palliative measure for certain advanced cancer patients.

Palliative care promotes symptom management and quality of life for terminal patients. A patient with a terminal cancer may no longer be a candidate for treatment; however, the patient may have weeks, perhaps months, to live. Several studies on survival rates of patients with advanced cancer noted extended survival improved for patients on home PN.[13,14] One study of ovarian cancer patients with short bowel obstruction treated for 75 days showed improvement with home PN vs pre-home PN rates.[13] Another study of cancer patients with GI obstruction revealed a longer survival rate, up to 1 year, and improved quality of life after cessation of active therapies.[14]

In the palliative setting, PN can extend survival; however, it is associated with risks such as line infections, fluid and electrolyte imbalances, and liver and pancreatic issues. There are general guidelines suggested for the use of PN in patients with advanced cancer.[15] First, standard oral diet or enteral nutrition is always the preferred form of nutrition. PN should only be used in patients with a nonfunctioning GI tract, if death will occur from starvation earlier than it would from disease progression, and the patient has a life expectancy of at least 2 to 3 months. Finally, parenteral nutrition improves quality of life for the patient in the last part of life. PN administration to patients with advanced cancer presents ethical and moral considerations that should be carefully considered when deciding on the care plan for cancer patients in the final stages of life. ■

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