Intravenous Hyperalimentation as an Adjunct to Cancer Patient Management

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Frequently, nutritional therapy is necessary as an adjunct to antineoplastic treatment because chemotherapy, radiotherapy, and surgery often limit enteral intake and result in malnutrition.

The gastrointestinal tract is the ideal system for digestion, absorption, and assimilation of nutrients; nevertheless, in the cancer patient, appetite may be poor, absorption may be inadequate, and access to the gut may be impossible or impractical, each of which interferes with rapid nutritional repletion via the enteral route. Because of a prohibitive degree of associated malnutrition, certain patients may be denied adequate oncologic therapy, and nutritional repletion via the alimentary tract may be impossible or inadvisable. Intravenous hyperalimentation (IVH) provides rapid nutritional restoration by vein.

Prior to 1972, IVH had not been applied to the treatment of a large number of cancer patients because of two potential problems: (1) tumor growth might have been stimulated by the potent nutritional solutions; and (2) septic complications might have resulted from the use of the indwelling superior vena cava catheters, necessary for the administration of IVH, in patients who had depressed leukocyte counts associated with chemotherapy or radiotherapy and who also had depressed immunocompetence secondary to oncologic treatment, tumor burden, or malnutrition.

In our laboratories, a series of animal experiments was designed to test the effects of malnutrition followed by adequate nutritional repletion on tumor growth, host body weight, and immunocompetence. Buffalo rats were sensitized to purified protein derivative (PPD) by an injection of complete Freund's adjuvant. All animals with positive reactions to PPD were inoculated in the flank with Morris hepatoma, and tumors were allowed to grow in size to approximately one cm. in diameter. At this point, each rat was protein-depleted by being fed a high carbohydrate, protein-free diet, otherwise complete in essential fatty acids, minerals, and vitamins. Animals immediately began to lose weight, and after two weeks, 70 percent of the animals had negative reactions to PPD. They were then randomized into three dietary groups: (1) continued high carbohydrate, protein-free diet; (2) normal rat chow diet; and (3) IVH. After one week on the respective diets, the rats were again injected with PPD, and 48 hours later they were sacrificed. No animals that continued to be fed a protein-free diet regained PPD reactivity, whereas

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almost all animals that received the normal oral diet or IVH became PPD reactive at the end of one week. Rats in the protein-free and normal diet groups continued to lose weight, and the average tumor weight at sacrifice was 9.9 gm. and 11.7 gm., respectively. IVH rats gained weight, and the average tumor weight at sacrifice was 12.9 gm. Although tumors in the nutritionally repleted animals were larger, tumor weight to body weight ratios were not significantly different in all animal groups tested. Thus, tumor growth had not been stimulated out of proportion to the nontumor host nutritional repletion by either a normal diet or IVH. Moreover, the IVH animals gained weight, whereas the normal diet animals continued to lose weight gradually. Nevertheless, both nutritional repletion groups were more vigorous and looked much healthier than the protein-free diet animals and they were immunocompetent. 1

On the basis of these studies, stimulation of tumor growth with IVH to the detriment of the host did not appear to be a problem. Similarly, immunocompetence was restored when these malnourished animals were nutritionally replenished. Therefore, resistance to infection should have been improved. Malnutrition depresses established cell-mediated immunity. 2 It is this mechanism that is immunologically effective against most viruses and fungi. Consequently, nutritional repletion with IVH might improve host defense mechanisms against these organisms rather than impose a problem because of the indwelling superior vena cava catheter.

From observations in animals and man, 3,4 the application of IVH as adjunctive nutritional therapy for the cancer patient appeared safe and efficacious. In 1972, our group developed the therapeutic philosophy that any cancer patient who has a lesion potentially responsive to oncologic treatment and who cannot be nutritionally rehabilitated and maintained by enteral means should be considered a candidate for IVH. Nutritional depletion was defined as a recent unintentional loss of 10 percent or more of body weight, a serum albumin concentration of less than 3.4 gm. percent and/or a negative reaction to a battery of recall skin-test antigens. Patients who satisfied any two of these three criteria and who had a reasonable chance of responding to appropriate oncologic therapy were candidates for IVH. Similarly, patients who had been treated previously and were incapable of adequate enteral nutrition because of the malnutrition imposed by previous therapy were candidates for rehabilitation with IVH. Also, nutritionally healthy patients whose treatment plan necessitated multiple courses of chemotherapy, possibly combined with radiotherapy or surgery, were IVH candidates in order to maintain their optimal nutritional status during treatment.

In the past five years, more than 1,000 patients have received IVH as adjunctive nutritional therapy at M.D. Anderson Hospital and Tumor Institute. Recently, 406 consecutive cancer patients in the Anderson series were reviewed. 5 Treatment categories were chemotherapy, 43 percent; general surgery, 24 percent; head and neck surgery, 10 percent; radiotherapy, 10 percent; fistulas, six percent; and supportive care, seven percent. Without IVH, the malnourished patients were considered poor candidates for any form of oncologic therapy because of the predictable increased risk of complications during treatment as a result of the severity of malnutrition. Hyperalimentation was infused for an average of 23.9 days; the average weight gained in these 406 patients during IVH was five lb. and 488 subclavian vein-feeding catheters were utilized. These catheters were not changed routinely. Indications for catheter removal were termination of the IVH treatment course, unexplained temperature elevation, a positive blood culture, or a mechanical problem with the catheter infusion system. Four hundred twenty subclavian vein catheters were cultured consecutively on removal. Pathogenic organisms were grown from 19 catheters (4.4 percent) (Table I); however, simultaneous positive blood and catheter cultures were obtained in only 10 patients (2.3 percent). In three
of these 10 patients, a primary source of the septicemia other than the catheter was identified. In the remaining seven patients (16 percent), the temperature returned to normal 48 hours after catheter removal, and it is in these patients that the catheters were incriminated as the primary source of organisms.

Chemotherapy

Intravenous hyperalimentation was utilized as an adjunct to chemotherapy in 175 patients. IVH was infused for an average period of 22.8 days and resulted in an average weight gain of 5.6 lb. (Fig. 1). Often, the patients did not need to go home between courses of chemotherapy to recover nutritionally because nutrition was maintained by IVH, and the next course of chemotherapy could begin immediately after the leukocyte count became normal, usually in seven to 10 days. As a preventive measure against malnutrition, IVH and chemotherapy were begun almost simultaneously; however, if significant malnutrition existed before chemotherapy, the IVH was administered at least seven to 10 days prior to chemotherapy. Whether mucositis and the symptoms of nausea and general malaise were reduced during IVH administration depended somewhat on the chemotherapeutic regimens employed. For example, gastrointestinal symptoms secondary to 5-FU administration were reduced, whereas vinblastine and bleomycin continued to produce severe stomatitis. Leukocyte depression below 2,500 cell/cu mm. occurred in 51.5 percent of patients for an average duration of 7.7 days. Neither the nadir nor duration of leukocyte depression appeared to be affected by IVH. Only four pathogenic organisms were grown from 212 consecutively cultured subclavian vein-feeding catheters. Only three patients had simultaneously positive blood and catheter cultures, an incidence of catheter-related sepsis of 1.4 percent.

A 50 percent or greater reduction in

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**TABLE 1. PATHOGENIC ORGANISMS CULTURED FROM 19 CATHETERS**

| Pathogenic Organism                      | Number of Positive Cultures |
|------------------------------------------|-----------------------------|
| Candida tropicalis                       | 5**                         |
| Staphylococcus aureus                    | 2**                         |
| Klebsiella pneumoniae                    | 2                           |
| Enterococcus                            | 2**                         |
| Escherichia coli                        | 2**                         |
| Alpha-hemolytic streptococcus           | 1                           |
| Candida albicans                        | 1                           |
| Proteus mirabilis                       | 1*                          |
| Pseudomonas aeruginosa                  | 1*                          |
| Enterobacter cloace                      | 1                           |
| Corynebacterium xerosis                 | 1                           |
| **Total**                               | **19**                      |

*Each asterisk represents one patient who had a positive catheter culture and simultaneous positive blood culture, same organism.*
A 22-year-old woman with widespread metastatic rhabdomyosarcoma primarily to the thoracic spine, pelvis, skull, liver, and retroperitoneum. At initial evaluation at M.D. Anderson Hospital, she weighed 92 lb and had a serum albumin concentration of 4.4 gm. percent. She was treated with cytoxan, vincristine, Adriamycin, and actinomycin-D (CYVADACT) and achieved a partial response but developed severe stomatitis and paralytic ileus. Her weight and serum albumin level fell to 82 lb. and 3.1 gm. percent, respectively. Right, Intravenous hyperalimentation was begun, and during the next 21 days, her weight rose to 104 lb. She continued to receive CYVADACT during IVH, and her metastatic disease continued to diminish. After discharge from the hospital, she maintained her weight through several subsequent courses of chemotherapy, and four months later she had a serum albumin of 4.4 gm. percent.

measurable tumor mass was obtained in 27.8 percent of these 175 patients. Responding patients survived an average period of 8.2 months, whereas nonresponding patients survived only 1.9 months. There may be a positive correlation between good nutritional status and potential for response to chemotherapy. Thirty patients with squamous cell carcinoma, adenocarcinoma, or undifferentiated carcinoma of the lung were evaluable for chemotherapeutic response. Each patient had extensive disease and was treated with the same drug protocol (bleomycin, cyclophosphamide, vincristine, methotrexate, and 5-FU). Ten of these patients were candidates for IVH and received a minimum of 2,000 kcal./day for an average of 22 days before, during, and immediately following administration of chemotherapy. All of these patients had lost six percent or more of their usual body weight before beginning therapy. Twenty patients did not receive IVH, although 12 of these patients also had lost more than six percent of their usual body weight. Five of 10 patients in the IVH group responded to chemotherapy, and the magnitude of prior weight loss appeared to have no adverse effects upon response. There were no responses in the non-IVH patient group when recent weight loss had been greater than six percent of the usual body weight; however, six of
eight patients who had lost less than six percent of their usual body weight responded to chemotherapy. The response advantages for the nutritionally intact patients were not explained on the basis of number of courses or doses of chemotherapy, or by distribution of histologic types, age, symptom status, prior treatment, or metastatic site. The data imply that the response rate was improved in patients who were adequately nourished at the outset of chemotherapy or who were nutritionally replenished with IVH during chemotherapy.

Since the advent of IVH and the concept of “bowel rest,” it has been possible to reduce significantly the physical, mechanical, and chemical trauma produced by the passage of food, digestive juices, and feces through the gastrointestinal tract. Application of IVH as an adjunct to cancer therapy with 5-FU should theoretically reduce both the incidence and degree of severity of gastrointestinal toxicity associated with this response. The concept of increased tolerance of 5-FU during bowel rest and nutritional maintenance with IVH was initially tested and confirmed in Sprague-Dawley rats.  

Information was then extrapolated to the human being, and the tolerance of 5-FU administered at a dose of 15 mg./kg./day in 50 ml. of five percent dextrose and water and infused over a one-hour period was studied in 26 cachectic, poor-risk patients with metastatic adenocarcinoma of the colon.  Sixteen of these patients were begun on IVH seven days prior to instituting 5-FU. As in the rats, drug toxicity was initially manifested by mild diarrhea, often accompanied with stomatitis and nausea. These symptoms cleared within 24 hours of discontinuing 5-FU therapy. The average total dose of 5-FU administered was 7.4 gm. during an average period of 8.6 days of treatment. Overall weight gain in these patients during IVH and 5-FU administration was 8.5 lb., and five patients (31 percent) responded with a greater than 50 percent reduction in measurable tumor volume.

Ten patients not treated with IVH lost an average of 4.2 lb. during 5-FU administration and experienced stomatitis, nausea, vomiting, and diarrhea in an average of only 4.4 days of chemotherapy. The average total dose of chemotherapy administered to these control patients was 3.8 gm. Only one non-IVH patient responded to chemotherapy. Conclusions from this study must be guarded because the patient groups were small; nevertheless, the application of “bowel rest” and total parenteral nutrition did appear to increase the tolerance of 5-FU in both rats and man, and malnourished patients who were nutritionally replenished prior to 5-FU experienced a greater response to chemotherapy (31 percent) than did patients who were not nutritionally replenished (10 percent).

**Radiotherapy**

Radiotherapy to the gastrointestinal tract may result in acute radiation enteritis so that patients ingest less food and are less able to digest and absorb those nutrients that do reach the small intestine. Some degree of radiation enteritis or stomatitis usually must be accepted for an adequate tumor dose of radiation to be delivered to a malignancy that lies within or near the alimentary tract. Although the acute effects of radiotherapy usually subside, malnutrition during treatment may be disabling, and radiotherapy may necessarily have to be discontinued before an adequate tumor dose has been administered.

Thirty-nine malnourished patients required treatment with IVH to complete a planned course of radiotherapy.  Intra-venous hyperalimentation was utilized for an average period of 37.6 days, and the average weight gain was 7.8 lb. Anorexia, nausea, and vomiting disappeared during IVH unless the patients attempted oral feeding, in which case all symptoms recurred. The average dose of radiotherapy delivered during IVH was 3827 rad in an average of 3.5 weeks. Ninety-five percent of the patients completed their planned course of radiotherapy and symptomatically improved. Fifty-four percent of the patients responded with greater than 50 percent reduction in tumor size. As with
TABLE 2. RESPONSE TO RADIOThERAPY

| Response                                    | Percent of Patients |
|---------------------------------------------|---------------------|
| Weight maintained; tumor response           | 44                  |
| No weight maintenance; tumor response       | 10                  |
| No weight maintenance; no tumor response    | 41                  |
| Deaths                                      | 5                   |

The chemotherapy patients, those patients responding to radiotherapy were able to maintain the weight gained during IVH after it was discontinued, but nonresponding patients promptly lost weight (Table 2). Responding patients gained an average of 13.0 ± 6.5 lb. during IVH and radiotherapy, compared with nonresponding patients who gained only 4.9 ± 8.8 lb. during a similar treatment course. Serum albumin rose from 3.12 ± 0.49 gm. percent to 3.51 ± 0.68 gm. percent during treatment of responding patients, but did not rise significantly from 3.09 ± 0.48 gm. percent in nonresponding patients. Thus, IVH allowed a planned course of radiotherapy to be delivered to a group of poor-risk, malnourished cancer patients, a positive correlation between tumor response and nutritional status was identified, and symptoms of radiation stomatitis and enteritis were reduced or eliminated as long as patients were not allowed enteral nutrition.

**Fistulas**

Fistulas in cancer patients present several unique problems because the fistula may involve an area of irradiated bowel or abdominal wall, there may be cancer in the fistulous tract, or the patient's life expectancy may be so short that the physician does not think the time needed to heal the fistula is justified particularly if the fistula is life threatening. Our experience with the management of fistulas in the cancer patient has been rewarding. Twenty-five patients with gastrointestinal fistulas have been treated with IVH. Spontaneous closures occurred in 44 percent of these patients after an average of 31.2 days of IVH, and successful surgical closure was obtained in seven patients (28 percent). Following closure, each patient returned home and was able to lead a productive life for at least a short period of time. In two patients, spontaneous closure occurred even though gastrointestinal cancer was present in biopsy specimens from the fistulous tract. Six patients developed pharyngocutaneous fistulas after radical head and neck surgery. Two of these fistulas closed spontaneously after 17 and 20 days of IVH. The remaining four fistulas were closed surgically after 21 to 47 days of IVH, and the average weight gained during this period was 15 lb. In three patients, surgical closures had failed prior to instituting IVH. In contrast, our results for spontaneous closure of enteric fistulas arising from irradiated bowel were uniformly poor. Although spontaneous fistula closure was achieved in several patients, each fistula eventually reopened, and the patient either
died or required operation. We recommend that patients who have radiation-related fistulas of the gastrointestinal tract be considered surgical candidates and, if malnourished, be prepared for an appropriate surgical procedure by utilizing IVH preoperatively for 10 to 21 days to stimulate weight gain and anabolism.

Surgery

One hundred patients received IVH preoperatively, postoperatively, or both as nutritional support for a general or thoracic surgical procedure. Major organ resections or procedures necessitating bowel anastomoses were done in 66 patients, whereas 34 patients underwent diagnostic or palliative procedures involving major surgical intervention. In each instance, the extent of malnutrition was such that recovery from these surgical procedures would have been questionable without intravenous nutritional rehabilitation. Overall, IVH was infused for an average period of 24.2 days, and the average weight gain during IVH was 4.2 lb. IVH was utilized for an average period of 12.3 days preoperatively and 13.9 days postoperatively. Increases in strength and weight gain, a significant rise in serum albumin concentration, and return of immunocompetence were much easier to accomplish with IVH preoperatively than postoperatively. Preoperatively, the average serum albumin concentration before IVH was 3.2 ± 0.41 gm. percent and rose to 3.77 ± 0.79 gm. percent prior to operation. Postoperatively, at the termination of IVH, average serum albumin concentration was 3.5 ± 0.60 gm. percent. Thus, albumin concentrations increased significantly preoperatively but with no further increase postoperatively. Weight gain during IVH followed a similar pattern. The failure to gain weight postoperatively in this group of patients might be indicative of the magnitude of stress associated with operative treatment, and without IVH, weight loss and major complications would have been expected because of the initial degree of malnutrition. Mortality in these 100 surgical patients was only four percent. Because there were so few surgical complications, we recommend that nutritional rehabilitation measures be instituted before operation instead of waiting until a catastrophic postoperative complication has occurred.

Although preoperative nutritional repletion is advisable, all too often, the surgeon encounters a patient who has developed a postoperative complication, such as an enterocutaneous fistula, prolonged ileus, gastric atony, intra-abdominal sepsis, wound disruption, or decubitus ulcer, which may be the result of, or will lead to, malnutrition. Intravenous hyperalimentation is indicated for the treatment of most of these conditions.

The need for hypocaloric feeding with 3.0 percent to 4.5 percent amino acid mixture without additional calories as glucose or fat has been infrequent in our patients. Although a certain amount of lean body mass may be spared during administration of peripheral amino acids, the efficacy of this treatment for patients with postoperative surgical complications has not been proved. Also, the preoperative use of peripheral amino acids as a means of nutritionally replenishing the malnourished surgical patient has not been demonstrated. Possibly, the remaining muscle mass in the malnourished patient is spared from further degradation as an energy source during hypocaloric feeding, but weight gain, restoration of lean body mass, and return of strength and immunocompetence require building blocks in the form of amino acids, vitamins and minerals, and an adequate exogenous caloric source such as glucose and possibly fat.

Patients with oropharyngeal malignant neoplasms present a special nutritional problem because they often have a history of heavy alcohol intake, smoking, and dietary irregularities. They may be undernourished and have vitamin deficiencies at the time that oropharyngeal malignancy develops, and the cancer may increase malnutrition if it produces obstruction or pain on deglutition. Nasogastric intubation and appropriate tube feedings will suffice to nutritionally replenish most of these patients, but sometimes such feedings are not tolerated because of re-
gurgitation or malabsorption, and weight gain is either not achieved or is minimal. Intravenous hyperalimentation was used in 39 patients with head and neck cancer who could not tolerate or did not respond to nasogastric tube feedings. Prompt nutritional repletion and weight gain were achieved in each patient. Nevertheless, four patients died postoperatively, probably because the magnitude of the surgical procedure exceeded their capability of wound healing. Malignant lesions of the head and neck may grow to a large size before metastasizing. These lesions can be anatomically removed, but because of the extent of the surgical resection, wound healing cannot be accomplished even after nutritional replenishment with IVH. Consequently, overzealous surgery should be avoided even though the patient appears to be “doing well” on IVH.

Three patients had pharyngeal incompetence after a major head and neck surgical procedure. In each instance, pharyngeal incompetence was thought to be secondary to muscle weakness and reversible muscle injury. Nutrition was maintained with IVH, and deglutitory muscular rehabilitation was begun. Weight gain of as much as 26 lb. was achieved, and with concomitant return of general body muscle strength and tone, swallowing function returned after 18 to 48 days of IVH.

Although catheter-related sepsis was an infrequent complication in our series of IVH patients, it was the most common complication in patients receiving IVH during treatment for head and neck malignancies. Secretions from pharyngostomy and tracheostomy stomas frequently contaminated the catheter dressings, and daily dressing changes were often necessary. A water-repellent sheet was placed over the dressings in an attempt to keep them dry. Seven (17.9 percent) patients had pathogenic organisms cultured from their feeding catheters. Four (10.3 percent) of these patients had simultaneous positive blood and catheter cultures associated with sepsis. To date, no deaths or complications secondary to catheter-related sepsis have occurred. Without IVH, some patients with head and neck cancer cannot be treated; however, IVH must be used cautiously and only when other forms of nutritional repletion have failed or are impractical.

Of these 139 surgical patients, few had postoperative complications related to infection and wound healing. An important indicator of adequate nutritional status, in our opinion, is reactivity to recall skin-test antigens. A patient whose preoperative nutritional status is questionable should be skin tested, and as a rule of thumb, if he has a negative reaction, preoperative nutritional repletion should be undertaken for at least seven to 10 days prior to operation. If the patient has a positive reaction to skin tests, the surgical procedure usually can be done safely without preoperative intravenous nutritional rehabilitation. For example, 14 surgical patients who did not have a disease impairing immune reactivity (such as Hodgkin’s disease or leukemia) and who were not receiving immunosuppressive drugs, e.g., corticosteroids, were skin tested prior to initiation of IVH and at seven to 10 day intervals throughout nutritional treatment. Four patients had negative test results throughout their course of IVH and one patient’s test converted to negative postoperatively. Three of these patients with negative reactions died and two had a prolonged postoperative recovery. The nine patients with positive reactions had an uncomplicated postoperative recovery period. In each of the patients who died, sepsis was a major contributor to death.

**Comment**

The use of IVH allowed specific antineoplastic therapy to be administered to a group of malnourished patients who otherwise might not have been acceptable candidates for intensive oncologic therapy. Septic complications were minimal and tumor growth was not stimulated. Nutritional repletion often resulted in a return of immunocompetence and was associated with a reduction in sepsis, proper wound healing and an apparent increase in tumor response to chemotherapy. For immunotherapy to be effective, the body's immunologic mechanisms must be functional.
Malnutrition depresses established delayed hypersensitivity, whereas humoral immunity is less severely affected. Multiple short courses of chemotherapy can limit the cellular response to a primary antigen but does not severely curtail established delayed hypersensitivity. If a malnourished patient receives chemotherapy, his primary and secondary cellular immune responses may be depressed and he becomes a vulnerable target for infection. Since leukocytes are depressed during most chemotherapy, a patient's resistance to invasion by all microorganisms is further reduced. Nutritional repletion will help restore established delayed hypersensitivity, a very important line of defense, particularly in adults who usually have previous immunity to most common microorganisms such as the Candida species and certain influenza viruses.

In a group of malnourished cancer patients receiving chemotherapy, our team recently demonstrated that previous negative reactions to a battery of recall skin-test antigens would convert to positive reactions in an average period of 11.4 days of nutritional therapy with IVH. 10 A significant reduction in tumor volume in response to chemotherapy occurred only in patients with positive skin-test reactions. Death occurred only in patients with negative skin-test reactions and was usually secondary to fungal sepsis. In a group of radiotherapy patients, conversion of skin-test reactions to positive during IVH was more difficult to achieve. These patients were receiving radiotherapy to the thymus or large segments of bone marrow or blood (i.e., the mediastinum, heart or pelvis). Possibly radiotherapy to these areas reduced the number or efficacy of circulating T-lymphocytes responsible for delayed cutaneous hypersensitivity. Although skin-test reactivity did not convert to positive in these patients, there were no complications secondary to radiotherapy, and nutritional rehabilitation with IVH was considered adequate.

Cancer cachexia should no longer be a contraindication to adequate oncologic therapy. Malnutrition should be prevented if possible and corrected when discovered in order to reduce surgical, chemotherapeutic, and radiotherapeutic morbidity and mortality, and to optimize the opportunity for response to treatment. Proper nutrients should be made available for use by the host to heal wounds, phagocytize cancer cells, repair immunologic mechanisms, replete protein stores, and restore enzyme systems to normal.

The field of cancer, nutrition, and immunity is in its infancy, and the investigation of the interrelationships between tumor and host metabolism are just beginning; nevertheless, enough data exist to indicate that the nutritionally healthy patient is a significantly better cancer therapy candidate than is his malnourished counterpart. When enteral nutritional repletion has failed, IVH may be efficacious and safe even in the leukopenic patient.

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