Nutrition as an Adjunct to Cancer Treatment in the Adult

Edward M. Copeland, III, John M. Daly, and Stanley J. Dudrick

Department of Surgery, The University of Texas Medical School at Houston [E. M. C., J. M. D., S. J. D.]; Department of Surgery, Hermann Hospital/The University Hospital [E. M. C., J. M. D., S. J. D.]; and The University of Texas System Cancer Center, The M. D. Anderson Hospital and Tumor Institute [E. M. C., S. J. D.], Houston, Texas 77030

Summary

Because of the fear of complications secondary to malnutrition, certain patients may be denied proper oncological therapy. With the advent of i.v. hyperalimentation (IVH) a technique became available which would allow rapid nutritional repletion of patients who otherwise could not be adequately nourished enterally. During a 3-year period, 406 cancer patients received IVH for 10 to 147 days (average, 23.9 days) as an adjunct to treatment. In 175 patients, chemotherapy was combined with IVH. Average weight gain was 5.6 lb, tumor response was obtained in 27.8% of patients, and leukocyte depression occurred in 51.5% of patients and lasted an average period of 7.7 days. A correlation between adequate nutritional status and response to chemotherapy was identified. Of the 100 surgical patients, 66 underwent major ablative procedures, and the mortality rate for the entire group was only 4%. Those patients who received IVH both pre- and postoperatively had few surgical complications and no mortality. Ninety-five % of the radiation therapy group completed their planned course of treatment, and 54% responded with a greater than 50% reduction in radiated tumor volume. Catheter-related sepsis occurred in only 1.6% of patients, tumor growth was not measurably enhanced by the nutritional solutions, and immunocompetence and tolerance for certain chemotherapeutic agents was improved.

Is nutritional therapy necessary as an adjunct to treatment of patient with cancer? The answer is clearly, yes. At some point during treatment of most malignant diseases, particularly when metastasis has occurred, malnutrition becomes a problem because many antineoplastic treatment modalities such as chemotherapy, surgery, and radiation therapy result in tissue injury and the consequent need for repair. When their initial diagnosis is made, most patients with cancer are not malnourished. Some patients, however, may have lost 5 to 10 pounds by that time because of anxiety over their symptoms, diminished oral intake secondary to pain on deglutition, or partial gastrointestinal obstruction or, possibly, altered metabolic demands of the malignant process. The latter possibility is poorly understood, and widely differing opinions and experimental results have been expressed in the literature. Certainly, patients with oat cell carcinoma of the lung lose weight rapidly and out of proportion to the increase in magnitude of the malignant process, whereas patients with metastatic melanoma or breast cancer can have widespread metastatic cancer and yet remain relatively well nourished. Nevertheless, with most malignant diseases, a deterioration of nutritional status usually parallels the increase in tumor volume.

Although the gastrointestinal tract is the ideal system for digestion, absorption, and assimilation of nutrients, appetite may be poor, absorption may be inadequate, and access to the gut may be impossible or impractical, each of which factors limits the capability of rapid nutritional repletion via the enteral route. Because of a prohibitive degree of associated malnutrition, certain patients may be denied adequate oncological therapy, and the possibility of nutritional repletion by utilizing the alimentary tract may not be available or advisable. With the advent of IVH a technique became available which could allow rapid nutritional restoration by vein to the extent that 2500 to 4000 calories, primarily as glucose, could be provided to the patient daily, together with the required amino acids, vitamins, and minerals.

Until 1974, IVH had not been applied to the treatment of a large number of cancer patients (2). There were 2 potential major problems which the use of IVH might have caused for the physician caring for these patients. First, tumor growth might have been stimulated by the potent nutritional solutions. Previous experimental work had shown that malnourished rats accepted tumor transplants much more poorly than their well-nourished controls, and the tumors of rats malnourished following the establishment of tumor growth were significantly smaller than tumors of control rats that were allowed to eat spontaneously and maintain adequate nutritional status. The 2nd major problem was the potential for septic complications secondary to the indwelling superior vena caval catheter, necessary for the administration of IVH, in patients who had depressed leukocyte counts associated with chemotherapy or radiation therapy and who also had depressed immunocompetence secondary either to oncological treatment, tumor burden, or malnutrition.

In our laboratory a series of experiments was designed to test the effects of malnutrition followed by adequate nutritional repletion on tumor growth, host body weight, and immunocompetence (3). The experimental model chosen for study was the Buffalo rat with a transplanted Morris 5123 hepatoma. Each animal was sensitized to PPD by an injection of complete Freund's adjuvant. All animals with positive reactions to PPD were inoculated with Morris hepa-
toma, and tumors were allowed to grow to the size of approximately 1 cm in diameter. At this point, each rat was fed a high-carbohydrate, protein-free diet. Animals immediately began to lose weight, and after 2 weeks, 70% of animals had negative reactions to PPD. They were then randomized into 3 dietary groups: (a) continued high-carbohydrate, protein-free diet; (b) normal rat chow diet; or (c) IVH. After 1 week on the respective diets, the rats again were given injections of PPD, and 48 hr later they were sacrificed. No animals that continued to be fed the protein-free diet regained PPD reactivity, whereas almost all animals receiving the normal oral diet or IVH became PPD reactive at the end of 1 week. All rats in the protein-free diet group continued to lose weight (average, —23 g), and the average tumor weight at sacrifice as 9.9 g. Normal-diet animals also continued to lose weight (average, —17 g), and tumor weight at sacrifice was 11.7 g. IVH rats gained weight (average, +14 g), and average tumor weight at sacrifice was 12.9 g. Although tumors in the nutritionally repleted animals were larger, tumor weight-to-body weight ratios were not significantly different in all groups. Thus, tumor growth had not been stimulated out of proportion to the non-tumor host nutritional repletion by either a normal diet or IVH. Moreover, the IVH animals gained weight, whereas the normal-diet animals continued their gradual declination in weight. Nevertheless, both nutritional repletion groups looked much healthier and more vigorous than the protein-free diet animals, and were immunocompetent.

On the basis of the above 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. During treatment with chemotherapy, many host defense mechanisms are depressed, and susceptibility to microorganisms is thereby increased. Chemotherapy, however, appears to depress only primary delayed hypersensitivity, whereas malnutrition depresses established cell-mediated immunity. This latter mechanism is immunologically effective against most viruses and fungi. Consequently, nutritional repletion with IVH might improve host-defense mechanisms against bacteria, viruses, and fungi rather than impose a problem because of the indwelling superior vena caval catheter.

Dudrick et al. (4) had previously shown that proper aseptic management of the indwelling catheter and IVH delivery system and aseptic mixing of the IVH solutions by the pharmacist minimized septic complications secondary to IVH in a noncancer patient population to an acceptable level. With the same techniques, IVH was used to treat 93 patients with a wide variety of malignant diseases (5). At the termination of IVH, each catheter tip was cultured for anaerobic and aerobic bacteria and fungi. One-half of the patients in this study received chemotherapy and had leukocyte count depressions below 2500 cells/μm for an average duration of 7.2 days. The average period of central venous catheterization was 24.8 days. No organisms were grown from catheters in place for less than 10 days, and 8 positive cultures (7.3%) were obtained from catheters in situ longer than 10 days. The catheter could be incriminated as the source of infection in only 2 patients (2.2%), both of whom had Candida albicans cultured from the catheter and the bloodstream. This low rate of microbial complications showed that IVH could be used successfully in cancer patients if strict adherence to aseptic techniques throughout the mixing and administration of IVH was followed. Each of these 93 patients was considered a poor candidate for any form of oncological therapy because of the increased risk of complications during treatment as a result of the severity of the malnutrition. Only 8 patients died during or immediately following IVH; the remaining patients tolerated a therapeutic course of chemotherapy or radiation therapy or a major surgical procedure which would have been potentially fatal without nutritional rehabilitation with IVH. From these observations, the application of IVH as adjunctive nutritional therapy for the cancer patient appeared safe and efficacious. The technique is now being utilized at our institution before, during, and after treatment with chemotherapy, radiotherapy, surgery, and/or immunotherapy. The remainder of this paper will deal with the indications, results, and possible future applications of IVH (and as a consequence, with nutritional repletion in general) as a tool within the therapeutic armamentarium of the oncologist.

Clinical Material

Nutritional depletion is defined by our team as a recent loss of 10 lb or more of body weight, a serum albumin concentration of less than 3.4 g/100 ml, and/or a negative reaction to a battery of recall skin test antigens. Each of the 406 patients (Table 1) in this series was an adult who had a reasonable chance of responding to adequate oncological therapy and either fulfilled the criteria for nutritional depletion or was a nutritionally healthy patient whose treatment plan would require multiple courses of chemotherapy, possibly combined with surgery or radiation therapy. The additional malnutrition that would result from this therapy was predictably dose limiting (6).

IVH was used as previously described (7), and insertion of the subclavian vein catheters and management of the IVH regimen were the responsibility of the IVH team. This included the authors, the resident staff, 3 registered nurses, and a trained pharmacist. Of the subclavian vein catheters utilized, 428 were cultured consecutively for aerobic and anaerobic bacteria and fungi. Response to chemotherapy or radiation therapy was defined as a 50% or greater reduction in measurable malignant disease. With the exception of patients with cancer of the colon who received high doses of 5-FU, no attempt was made to administer the maximum tolerated dose of chemotherapy, but rather a dose which

<table>
<thead>
<tr>
<th>Indications for IVH</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>175</td>
</tr>
<tr>
<td>General Surgery</td>
<td>100</td>
</tr>
<tr>
<td>Head and neck surgery</td>
<td>39</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>39</td>
</tr>
<tr>
<td>Enteric fistulas</td>
<td>25</td>
</tr>
<tr>
<td>Supportive care</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>406</td>
</tr>
</tbody>
</table>

Table 1
was considered therapeutic by the medical oncology service at The University of Texas Systems Cancer Center M. D. Anderson Hospital and Tumor Institute.

Chemotherapy

IVH was used as an adjunct to chemotherapy in 175 patients. IVH was utilized for an average period of 22.8 days and resulted in an average weight gain of 5.6 lb. Patients completed a planned course of chemotherapy, and tumor response was obtained in 27.8% of patients. Responding patients survived an average time of 8.2 months, whereas nonresponding patients survived only 1.9 months (Table 2). Only those patients whose malignant diseases were potentially responsive to chemotherapy were selected for i.v. nutritional replacement. Patients who had received all reasonable antineoplastic treatment and failed to respond were not considered IVH candidates. If a response to chemotherapy was obtained, patients had minimal difficulty maintaining their weight following discharge from the hospital, and often IVH was unnecessary as an adjunct for subsequent courses of chemotherapy. Whether or not mucositis and the symptoms of nausea and general malaise were reduced during IVH administration depended somewhat upon the chemotherapeutic regimen used. For example, gastrointestinal symptoms secondary to 5-FU administration were reduced, whereas vinblastine and bleomycin continued to produce severe stomatitis.

Leukocyte depressions below 2500 cells/cu mm occurred in 51.5% of patients and lasted for an average period of 7.7 days. Neither the nadir nor duration of leukocyte depression appeared to be affected by IVH. Only 4 pathogenic organisms were grown from 212 consecutively cultured subclavian vein catheters used in the chemotherapy patient group. Only 3 patients had simultaneous positive blood and catheter cultures, an incidence of catheter-related sepsis of 1.4%.

There was a positive correlation between nutritional status and response to chemotherapy in 30 patients with nonsept cell carcinoma of the lung who received the same treatment protocol (bleomycin, cyclophosphamide, 5-FU, methotrexate, and vincristine) (8). The IVH team was consulted to treat 10 of these patients, each of whom had lost more than 6% of his usual body weight prior to beginning oncological therapy. Twenty patients did not receive IVH, although 12 of these patients also had lost more than 8% of their usual body weight. In the IVH group, 5 of the 10 patients responded to chemotherapy, and the magnitude of their prior weight loss appeared to have no adverse effect upon response. However, there were no responses in the non-IVH patient group whose recent weight loss had been greater than 6% of the usual body weight. Six of the 8 patients who had lost less than 6% of their usual body weight responded to chemotherapy. These data imply that response rates were improved when patients were adequately nourished at the onset of chemotherapy.

An increased tolerance for 5-FU was demonstrated in rats maintained on IVH (9). Administration of 5-FU, 15 mg/kg/day i.p., for 7 days killed 80% of rats fed p.o., whereas only 30% of animals nutritionally maintained solely by IVH were killed by the same dose of 5-FU. This experience was applied clinically to human beings, and 16 patients with metastatic colon cancer, susceptible to evaluation for chemotherapeutic response, were given IVH for 7 days before beginning treatment with 5-FU (15 mg/kg/day diluted in 50 ml of 5% dextrose and water and delivered i.v. over a 1-hr interval). Ten control patients had similar disease patterns and degrees of malnutrition but did not receive IVH. Conclusions from this study must be guarded because the patient groups are small; nevertheless, treatment with IVH during 5-FU administration did result in weight gain, increased tolerance for the drug, and a better tumor response rate (Table 3).

IVH has been used as prophylaxis against weight loss produced by treatment with vinblastine and bleomycin. Using IVH and this drug combination, a 50% complete response rate has been obtained in a group of young, adult, nutritionally healthy males with metastatic embryonal cell carcinoma of the testicle. Throughout multiple back-to-back chemotherapy courses, weight loss was prevented and strength was maintained, even though symptoms of stomatitis and general malaise were severe. When these data were compared with tumor response data in similar patients with the same disease treated according to the same drug protocol but who did not receive IVH, it was noted that the response rates of IVH and non-IVH patients were the same, as were the survival times of the responding patients. However, the survival times of the nonresponding IVH patients were significantly greater than those of nonresponding patients who did not receive IVH during chemotherapy. In the latter group, weight loss of from 10 to 40 pounds occurred during chemotherapy, and these patients were exposed to the side effects of nutritional depletion as well as to growing malignant disease. No doubt the IVH patients who were nutritionally sound could deal better with the problems of increasing tumor mass than could their debilitated counterparts and thus enjoyed a longer survival.

Table 2

<table>
<thead>
<tr>
<th>Site or origin</th>
<th>No. of patients</th>
<th>% response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>Lung</td>
<td>34</td>
<td>29</td>
</tr>
<tr>
<td>Testicle</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>(no 5-FU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>(5-FU)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head and neck</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Leukemia</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>13</td>
<td>23</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>13</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Hyperalimentation and 5-FU</th>
<th>Chemo-therapy (days)</th>
<th>Total dose of 5-FU (g)</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVH*</td>
<td>+8.4</td>
<td>8.6</td>
<td>7.4</td>
</tr>
<tr>
<td>Controls*</td>
<td>−4.2</td>
<td>4.4</td>
<td>3.8</td>
</tr>
</tbody>
</table>

* Sixteen patients were treated for 23.9 days.

† Ten patients.
Surgery

One hundred patients received IVH as nutritional support for general or thoracic surgical procedures. Sixty-six patients underwent major organ resections or procedures requiring bowel anastomosis, and 34 patients underwent palliative or diagnostic procedures that required major surgical intervention. Fifty-two % of patients had curative resections that included total gastrectomies, esophagectomies, and abdominal-perineal resections. Without i.v. nutritional re- habilitation, recovery from these surgical procedures would have been questionable in each instance. The average age of the patients was 56.5 years, IVH was utilized for an average period of 24.2 days, and average weight gained during IVH was 4.2 pounds. In 57 patients, IVH was utilized for an average period of 12.3 days preoperatively and 13.9 days postoperatively. Thirty-two patients received IVH only postoperatively for an average period of 18.9 days, and 11 patients received IVH only preoperatively for an average period of 18.1 days. Weight gain, increase in strength, significant rise in serum albumin concentration, and return of immunocompetence were much easier to accomplish with IVH preoperatively than postoperatively. Those patients who received IVH both preoperatively and postoperatively had fewer surgical complications and were usually eating within 4 to 5 days after bowel resection. Those patients who received IVH only postoperatively usually had developed one of the complications of prolonged inanition, such as pneumonia, wound infection, paralytic ileus, decubitus ulcer, or wound dehiscence before IVH was instituted. Because patients who were nutritionally replenished preoperatively had so few surgical complications, we recommend strongly that measures to correct malnutrition be instituted before operation rather than waiting until a catastrophic postoperative complication has occurred before thinking of nutritional restoration. Four patients in this series died. Two died of pneumonia, 1 after right colectomy and the other after esophagectomy. Two died of myocardial infarction following exploratory laparotomy and operative bypass of a radiation-related enteric fistula. The mortality rate of 4% for this group is rather respectable, considering the magnitude of the surgical procedures and the debilitated initial condition of the patients.

Radiation Therapy

Patients receiving radiation therapy to the gastrointestinal tract often become anorectic, and the mucositis secondary to radiation can produce pain on deglutition, crampy abdominal pain, nausea, and diarrhea. Radiation at times may cause edema of the bowel wall and obstruction of an already partially compromised gastrointestinal lumen. The net result of acute radiation enteritis is that the patient ingests less food and is less able to digest and absorb those nutrients that do reach the small intestine. Unfortunately, some degree of radiation enteritis or stomatitis usually must be accepted in order for an adequate tumor dose of radiation therapy to be delivered to a cancer that lies within or near the alimentary tract. Although the acute effects of radiation subside, malnutrition during therapy may be disabling, and radiotherapy may necessarily have to be discon-
were initially skin test negative. Thirteen of these patients converted their skin tests to positive during an average period of 11.4 days of IVH. Response to chemotherapy occurred only in those patients whose skin tests were positive, and conversion of skin tests to positive occurred before clinical regression of metastatic disease. No patient who received radiation therapy developed or retained positive reactions to skin tests, even though nutritional repletion was considered adequate. Ten patients received IVH as nutritional support for a major surgical procedure. Six patients maintained positive skin tests both pre- and postoperatively and had uncomplicated postoperative recoveries. Three patients remained negative throughout the pre- and postoperative periods, and 1 patient converted skin tests from positive to negative postoperatively. Two of these negative reactors died, and the other 2 had prolonged postoperative recovery periods complicated by pneumonia, ileus, and marked weakness.

Conclusions drawn from this study were that absence of established delayed hypersensitivity in the cancer patient who is treated with chemotherapy or surgery may be secondary to generalized malnutrition, and that established cell-mediated immunity may be restored by proper nutritional repletion.

Complications

In these 406 patients, complications from IVH were few (Table 6). Pathogenic organisms were grown from 19 of 428 consecutively cultured catheters (Table 7). Simultaneous positive blood and catheter cultures were obtained in only 10 patients (2.5%); in 3 of these 10 patients, a primary source of septicemia other than the catheter was identified, and in the remaining 7 patients (1.6%), temperature returned to normal within 48 hr of catheter removal. Staphylococcus epidermidis, diphtheroids, and Propionibacterium acnes were cultured from 21 catheters. In each instance, the positive catheter culture was incidental, there was no associated fever or positive blood culture, and the catheters were removed because of routine termination of IVH. Although these organisms may be infectious, no evidence of infection was found in these patients. Consequently, the organisms were thought to be skin contaminants.

Comment

Nutritional support of patients receiving oncological therapy has proved effective in allowing adequate treatment programs to be carried out in a series of patients who otherwise might not have been candidates for any form of antineoplastic therapy. Tumor growth was not measurably enhanced, and septic complications were minimal. There seemed to be a correlation between adequate nutrition and the potential for tumor response to chemotherapy. Moreover, it appeared that there was an increased tolerance for certain chemotherapeutic drugs, particularly 5-FU, and that the tumor response to these drugs might be improved because more drug could be delivered per unit of time. With current emphasis on immunotherapy, interrelationships between the body’s immune mechanisms and nutritional sta-

References

4. Wilmore, D. W., and Dudrick, S. J. Safe Long-term Venous Catheteriza-

Table 6

<table>
<thead>
<tr>
<th>Complication</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter-related sepsis</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>4</td>
</tr>
<tr>
<td>Subclavian vein thrombosis</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
</tr>
<tr>
<td>Jugular vein thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Symptomatic hypophosphatemia</td>
<td>1</td>
</tr>
<tr>
<td>Hyperchloremic metabolic acidosis</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>19 (4.7%)</td>
</tr>
</tbody>
</table>

Table 7

<table>
<thead>
<tr>
<th>Pathogenic Organism</th>
<th>No. of positive cultures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida tropicalis</td>
<td>5(^a)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2(^a)</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>2</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2(^a)</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>2(^a)</td>
</tr>
<tr>
<td>Alpha streptococcus</td>
<td>1</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>1</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1(^a)</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>1(^a)</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1(^a)</td>
</tr>
<tr>
<td>Corynebacterium xerosis</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
</tr>
</tbody>
</table>

\(^a\) Simultaneous positive blood culture, same organism. Temperature went down immediately after catheter was removed.
E. M. Copeland, Ill, et al.

Nutrition as an Adjunct to Cancer Treatment in the Adult
Edward M. Copeland III, John M. Daly and Stanley J. Dudrick


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/37/7_Part_2/2451

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact
the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact
the AACR Publications Department at permissions@aacr.org.