Nutritional Support of Bone Marrow Transplant Recipients: A Prospective, Randomized Clinical Trial Comparing Total Parenteral Nutrition to an Enteral Feeding Program

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ABSTRACT

Although standard supportive care for bone marrow transplant (BMT) recipients includes total parenteral nutrition (TPN), it has not been shown that this is the most appropriate method of nutritional support. To determine whether current BMT recipients require TPN during the early recovery period, we conducted a prospective, randomized clinical trial comparing TPN and an individualized enteral feeding program (counseling, high protein snacks and/or tube feeding). Nutritional assessment included measurement of serum proteins, anthropometry, and body composition analysis. For the latter, total body water and extracellular fluid were measured by standard radiodilution techniques and used to calculate body cell mass and body fat plus extracellular solids (FAT + ECS). In 27 TPN patients, body composition 28 days after BMT, expressed as a percentage of baseline, was body cell mass, 100%, extracellular fluid, 108%, FAT + ECS, 108%, and in 30 enteral feeding program patients, was body cell mass, 93%, extracellular fluid, 104%, and FAT + ECS, 94%. Only the difference in FAT + ECS was statistically significant (p < 0.01). Compared to the enteral feeding program, TPN was associated with more days of diuretic use, more frequent hyperglycemia, and more frequent catheter removal (prompted by catheter-related complications), but less frequent hypomagnesemia. There were no significant differences in the rate of hematopoietic recovery, length of hospitalization, or survival, but nutrition-related costs were 2.3 times greater in the TPN group. We conclude that TPN is not clearly superior to individualized enteral feeding and recommend that TPN be reserved for BMT patients who demonstrate intolerance to enteral feeding.

INTRODUCTION

BMT is a rigorous therapeutic modality used for the treatment of patients with severe aplastic anemia, leukemia, and certain other malignancies (1-3). The cytotoxic regimens designed to cure patients with these diseases are so intensive that without bone marrow rescue, the regimens produce lethal bone marrow failure. Individuals undergoing bone marrow transplantation do not usually eat adequate p.o. diets because of the adverse nutritional consequences associated with BMT. These toxicities, which include anorexia, fever, nausea, vomiting, mucositis, and diarrhea may be due to the preparative cytoreductive chemotherapy and total body irradiation, infection, or graft-versus-host disease (4-6). Since right atrial catheters for i.v. access have been demonstrated to be safe and well-tolerated by BMT recipients, standard supportive care now includes TPN.

It has not been shown that TPN is required by all bone marrow transplant recipients to recover hematological and immunological function. In fact, marrow grafts are successful in well-nourished mice unless they are totally deprived of protein and energy after BMT (4). Furthermore, TPN is an expensive therapeutic modality that is associated with risks and toxicities such as injury during catheter placement, volume overload, venous thrombosis, and infection. Nutritional support by the enteral route, however, eliminates the toxicities and costs specifically due to TPN. With individualized nutritional support programs that take advantage of current enteral feeding technology (e.g., one-on-one counseling, meal-by-meal menu selection, positive reinforcement techniques, specially prepared between meal snacks, commercial supplements, and tube feeding), it may be possible to use the enteral route to support patients recovering from BMT.

One of the greatest problems confronting the physician prescribing therapeutic nutrition is the lack of sensitive and practical methods to monitor the effects of nutritional therapy. Changes in body composition have obvious value as indicators of changes in overall nutritional status for patients who undergo nutritionally depleting therapies or who receive therapeutic nutritional support (8). Anthropometric measurements (skinfold thickness and limb circumference) are frequently used to determine body composition, but this method has been criticized as insensitive, error prone, and inaccurate (9, 10). In addition, standards have not been clearly established (11). More sophisticated methods such as neutron activation analysis (12, 13), underwater-weighing (14, 15), and determination of total body potassium by measurement of 40K (16, 17) are impractical in acutely ill hospitalized patients. We have shown (18, 19), however, that isotope dilution analysis of body composition (8) can be used effectively in such patients.

In this study of BMT recipients, we compared TPN and an individualized EFP for their effectiveness in preserving body composition and for clinical outcomes including frequency of catheter-related complications, medication use, abnormalities in serum chemistries, rate of bone marrow recovery, length of hospitalization, survival, and cost.

MATERIALS AND METHODS

Patient Population

This study was approved by the Joint Committee on Clinical Investigations of the Johns Hopkins University School of Medicine, and written consent was obtained from all patients or their guardians after they were informed of the nature, purpose, and possible risks involved with the study. The study was conducted from January 1, 1984 through July 10, 1986; patients 10-58 years of age were enrolled during the calendar year 1984. Minimum follow-up was 555 days. Patients were stratified by type of transplant (allogeneic or autologous) and randomized to one of the two feeding methods (TPN or EFP).
Bone Marrow Transplantation

Bone marrow transplantation was carried out according to standard protocols as previously described (1–3). Briefly, patients were treated with high dose chemotherapy (busulfan and/or cyclophosphamide) with or without total body irradiation, followed by infusion of bone marrow from a histocompatible donor or by reinfusion of previously cryopreserved autologous bone marrow. In addition to nutritional support, standard supportive care during the recovery phase included reverse isolation, antimicrobial therapy, blood product support, and physical therapy. By convention, the day of transplant is designated "day 0", days before transplant "minus days", and days following transplant "plus days" (e.g., day –1 is the day before BMT; day 7 is 1 week following BMT).

Study Protocol

The baseline body composition analysis and standard nutritional assessment were performed following randomization and before the day of BMT. The assigned nutritional therapies were started on day –1 and continued through day 28 unless the patient was discharged or died before day 28, or unless the patient was declared a treatment failure (see below). Patients failing the assigned nutritional treatment arm received the alternate treatment for the remainder of the study. Repeat body composition analysis and nutritional assessment studies were performed on day 10 ± 1 (SD) day and on day 28 ± 1 day after BMT. Patients were monitored daily for nutrient intake, potential treatment-related toxicities, and clinical outcome parameters (e.g., WBC, absolute neutrophil count, infection status). Data on patient infections were collected by epidemiologists who were blind with respect to treatment group assignments. Infectious episodes were scored using accepted criteria (20) for oncology patients.

In order to have venous access adequate for the infusion of antibiotics, blood products, cyclosporine, and the TPN solution, all patients assigned to the TPN group had two lumens. All autologous patients had two lumens. All patients had single and/or double lumen in-dwelling Silastic central venous Hickman-Broviac catheters placed before day –1. In addition, polyurethane central venous catheters were placed percutaneously without tunneling in eight TPN and one EFP patient.

Treatment Groups

Total Parenteral Nutrition. TPN patients received 35 kcal/kg/day and 1.4 g protein/kg/day from the standard TPN solution. This solution contained 25% dextrose, 4.25% amino acids (Fremaine III; Kendall McGaw), electrolytes, vitamins (MVI-12; USV Laboratories), and trace minerals (MTE-4; LyphoMed). The nutrient prescription and/or composition of the TPN solution was modified when clinically indicated (e.g., nutrients were concentrated to reduce the fluid intake in patients with fluid overload). TPN patients were allowed to eat ad libitum. When the patient's p.o. intake of protein was >0.5 g/kg/day for an evaluation period (3–4 days), the TPN intake was reduced. The patient was considered a treatment failure and crossed over to the EFP if, because of infection or malfunction, the central venous catheter had to be removed and could not be replaced.

Enteral Feeding Program. The EFP was an individualized program designed to provide at least the minimum nutrient intake necessary to support immunological and early immunological reconstitution while taking into consideration the preferences of individual patients. Nutrient goals were the same as those for TPN patients. Depending on the needs of particular patients, the nutritional care plan might have included one-on-one counseling, meal-by-meal menu selection, positive reinforcement techniques, special between-meal snacks, commercial supplements, or tube feeding. All patients received p.o. daily vitamin/mineral supplements (Daily-M: Upsher-Smith).

Patients whose voluntary p.o. intake of protein was <0.5 g/kg/day for an evaluation period (3–4 days) were prescribed protein-rich between-meal snacks. In addition, to ensure that the regenerating bone marrow had an adequate supply of amino acids, these patients received i.v. amino acids (0.5 g/kg/day) until their p.o. protein intake exceeded 0.5 g/kg/day or until they were declared treatment failures. Patients whose voluntary p.o. intake continued to be inadequate after day 10 were candidates for nasoenteric tube feeding. If the minimum protein intake could not be achieved by the combination of the voluntary p.o. and nasoenteric routes or when the enteral route was contraindicated, the patient was considered an enteral feeding failure and given TPN.

Standard Nutritional Assessment

The standard nutritional assessment included body weight, percentage ideal body weight (21, 22), serum albumin and transferrin concentrations, arm muscle and arm fat areas, total body fat estimated from measured tricipes and biceps skinfold thicknesses (24, 25), and estimation of body cell mass from measured creatinine excretion (26).

Isotope Dilution Analysis of Body Composition

In a model of body composition modified from the descriptions of Moore (8) and Shizgal (27), body mass is composed of three major compartments: ECF; BCM, the metabolically active, functional cell mass; and FAT + ECS. In addition to body fat, the FAT + ECS compartment includes the dry bone, fascia, and tendons, which were assumed to be of relatively constant size over the planned 28-day study period. Therefore, changes in the FAT + ECS compartment were attributed to changes in body fat.

Body composition was measured by isotope dilution analysis (8, 18). Total body water and ECF were measured using tritiated water ($^3$H$_2$O, 7 µCi/kg body weight) and [$^{169}$Yb]$^2$diethylenetriaminepentaacetate, 0.5 µCi/kg body weight), respectively, as tracers. Tracers were injected sequentially into the patient's i.v. catheter, and samples of blood were drawn 2, 2.5, 3, 3.5, and 4 h later. Triplicate samples of the tracers and plasma were assayed in a two-channel liquid scintillation counter. The $^3$H activity was corrected for the contribution of $^{169}$Yb activity. $^{169}$Yb activity was measured in a well-type gamma counter. The volume of tracer dilution was calculated using the formula of Chien and Gregersen (28)

$\frac{\text{Activity administered}}{100} - \frac{0.073}{100} \times \text{plasma total protein, g/dl} \times \text{Activity/g plasma} \times 100$

The factor [$100 - 0.073(\text{plasma total protein, g/dl})]/100$ represents the correction factor for plasma water (proteins act as solids, reducing the fluid and electrolyte content in a given volume of plasma). The figure for activity/g plasma was determined by extrapolating to time = 0 the plasma $^3$H and $^{169}$Yb activities measured during the equilibrium phase (2–4 h after tracer administration). This extrapolated value represents the presumed tracer activity had isotope dilution been instantaneous.

The sizes of the other body compartments were determined as

Intracellular fluid (kg) = Total body water (kg) – ECF (kg)

BCM = Intracellular fluid (kg) * 0.70

FAT + ECS (kg) = [Body weight (kg)] – [BCM (kg) + ECF (kg)]

The calculation of BCM from ECF was based on the assumption that 70% of cell mass can be attributed to water (29–31). The whole-body radiation absorbed dose per body composition study was approximately 30 mrad.

Data Analysis

The primary nutritional outcomes were changes in the sizes of the BCM, ECF, and FAT + ECS compartments that occurred from baseline to day 28. Secondary outcomes included changes measured by other nutritional assessment parameters. Day 28 values were expressed as a percentage of baseline, and between-group differences were evaluated by Student's t test (32). All tests were two tailed and $P < 0.05$ was considered to be statistically significant. Treatment-related differences in clinical outcome parameters (e.g., catheter-related complications, infections, bone marrow transplant, and other treatment-related toxicities) were considered to be statistically significant. Treatment-related differences in clinical outcome parameters (e.g., catheter-related complications, infections, bone marrow transplant, and other treatment-related toxicities) were considered to be statistically significant.
rate of hematopoietic recovery, medication use, and length of hospitalization were evaluated by \( t \) and Fisher's Exact (33) tests, as appropriate. We have reported the mean ± SD and the \( P \) for the \( t \) test, unless otherwise indicated.

Catheter-associated infection rates were evaluated by testing the equality of the two Poisson means (34). Nonparametric methods for otherwise indicated.

The results of the 61 patients who could be evaluated on day 28, one patient died too early to be evaluated (day 11), and the other was removed from the study because of major protocol violations. During the period of this study, there were no instances of TPN failure once i.v. feeding had been started. In each case where infection or mechanical complications resulted in the removal of a patient's central venous catheter, it was possible to replace the catheter and continue feeding.

Of the 30 patients randomized to the EFP, there were seven (23%) whose voluntary p.o. intake of protein was consistently <0.5 g/kg/day. Three of these patients were not candidates for tube feeding because of severe nausea and vomiting or diarrhea. In four patients, tube feeding was attempted, but unsuccessful (in three patients, because of nausea, vomiting or diarrhea; one patient refused tube feeding). These seven patients were crossed over to the EFP and did not receive TPN. Two of the four were evaluated on day 28, one patient died too early to be evaluated (day 11), and the other was removed from the study because of protocol violations. During the period of this study, there were no instances of TPN failure once i.v. feeding had been started.

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There were no demographic or baseline nutritional status characteristics that could be used to predict which patients were likely to fail either TPN or the EFP. In addition, EFP failures could not be identified from changes in nutritional status that occurred from baseline to day 10 (data not shown).

Data were analyzed in two ways: in the more conservative analytical approach, patients were analyzed according to their originally assigned groups; in the second analysis, the TPN failures who never received TPN and who could be evaluated on day 28 were analyzed with the group of patients originally assigned to the EFP. The magnitude and direction of the observed treatment-related differences were the same, irrespective of the analytical method. Only the results of the latter method have been reported below.

Energy and Protein Intakes. The total intake (i.v. plus enteral) and enteral intake of energy and protein were compared by BMT day for the 30 patients who actually received the EFP and the 27 TPN patients who were not declared TPN failures. Mean p.o. intakes were similar (15 kcal/kg/day; 0.4 g protein/kg/day) during the week before BMT; but following transplant, the p.o. intake of EFP patients was 15-20 kcal/kg/day and 0.1-0.4 g protein/kg/day. However, the

### Table 1 Demographic characteristics of the participating 31 TPN and 30 EFP patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPN</th>
<th>EFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous leukemia</td>
<td>9 (8)*</td>
<td>9</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>10 (9)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>4</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Preparative regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan-cyclophosphamide</td>
<td>10 (8)</td>
<td>12</td>
</tr>
<tr>
<td>Cyclophosphamide-total body irradiation</td>
<td>18</td>
<td>15 (13)</td>
</tr>
<tr>
<td>Cyclophosphamide-cyclosporine</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (≥19 yr)</td>
<td>21 (19)</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Child (&lt;19 yr)</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (13)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>Female</td>
<td>17 (16)</td>
<td>12</td>
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<tr>
<td>Race</td>
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<td></td>
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<tr>
<td>White</td>
<td>25 (23)</td>
<td>29 (27)</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Type of transplant</td>
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<td></td>
</tr>
<tr>
<td>Allogeneic</td>
<td>23 (21)</td>
<td>23 (22)</td>
</tr>
<tr>
<td>Autologous</td>
<td>8</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Remission no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>6 (5)</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>3 (2)</td>
</tr>
<tr>
<td>3+</td>
<td>14 (13)</td>
<td>16 (15)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, the 57 patients who could be evaluated on day 28.

* Other: six aplastic anemia; six non-Hodgkin's lymphoma; one breast cancer; one rhabdomyosarcoma; one malignant histiocytosis; one preleukemia.

### Table 2 Baseline nutritional status of the 61 patients as originally assigned

<table>
<thead>
<tr>
<th>Variable</th>
<th>TPN</th>
<th>EFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition (% body wt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body cell mass</td>
<td>47 ± 8*</td>
<td>50 ± 9</td>
</tr>
<tr>
<td>Extracellular fluid</td>
<td>27 ± 6</td>
<td>25 ± 5</td>
</tr>
<tr>
<td>Fat + extracellular solids</td>
<td>30 ± 10</td>
<td>26 ± 9</td>
</tr>
<tr>
<td>Anthropometry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm muscle area (% standard)</td>
<td>95 ± 21</td>
<td>88 ± 23</td>
</tr>
<tr>
<td>Arm fat area (% standard)</td>
<td>108 ± 44</td>
<td>101 ± 57</td>
</tr>
<tr>
<td>Total body fat (% body wt)</td>
<td>28 ± 8</td>
<td>25 ± 7</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>3.8 ± 0.4</td>
<td>3.9 ± 0.5</td>
</tr>
<tr>
<td>Serum transferrin (mg/dl)</td>
<td>204 ± 42</td>
<td>219 ± 39</td>
</tr>
<tr>
<td>% ideal body wt</td>
<td>105 ± 13</td>
<td>107 ± 11</td>
</tr>
<tr>
<td>% usual wt</td>
<td>94 ± 10</td>
<td>96 ± 7</td>
</tr>
<tr>
<td>Lean body mass from creatinine excretion (% body wt)</td>
<td>69 ± 20</td>
<td>68 ± 19</td>
</tr>
</tbody>
</table>

* Mean ± SD.
total intake of EFP patients was about one-half that of TPN patients (20–25 kcal/kg/day and 0.5–1.0 g protein/kg/day in EFP patients; 40–45 kcal/kg/day, 1.4–1.6 g protein/kg/day in TPN patients). Twenty-two (73%) EFP patients required i.v. amino acid supplements for an average of 7 ± 5 days. The mean total intake of i.v. amino acid supplements in these EFP patients was 0.1 ± 0.1 g/kg/day as compared to 1.3 ± 0.3 g/kg/day in TPN patients.

Changes in Nutritional Status. Although baseline body weight was similar in both treatment groups, patients in the TPN group gradually gained weight, whereas patients in the EFP group lost weight. In the TPN group, body weight on day 28 was 108 ± 9% of baseline; in the EFP group, body weight was 96 ± 5% of baseline ($P < 0.0001$). TPN patients gained weight primarily in the FAT + ECS and ECF compartments. EFP patients lost weight from both the BCM and FAT + ECS compartments, while the ECF compartment expanded slightly (Fig. 1). Of the treatment-related differences, only those in FAT + ECS and total body weight were statistically significant ($P < 0.01$). With 95% confidence, the true change in BCM from baseline to day 28 in EFP patients could have been a loss of 1–13% and for TPN patients a gain of 4% to a loss of 4%. These body composition changes (from baseline to day 28) were also detected by the standard nutritional assessment (Fig. 2); however, the changes were within the error of measurement. In both treatment groups, the serum concentrations of albumin and transferrin fell equally to 90–92% of baseline.

When TPN patients were compared with only those EFP patients who did not fail the program, the direction and magnitude of the differences were the same as those seen when TPN patients were compared with all EFP patients. There were no significant differences in BCM and body weight on day 28 in those EFP patients who failed the feeding program and in those who did not fail. However, patients who failed the EFP lost less fat (100 ± 28% of baseline versus 86 ± 13%) and TBW (100 ± 10% of baseline versus 97 ± 7%) than did patients who did not fail the EFP, although the differences were not statistically significant.

Medication Use. There were no treatment-related differences in the total number of days of analgesic, antiemetic, or i.v. antibiotic use during the 28-day study period. TPN patients received diuretics more frequently than did EFP patients (11 ± 6 days for TPN patients; 4 ± 5 days for EFP patients; $P < 0.0001$). TPN patients required exogenous insulin for 8 ± 11 days, while EFP patients required supplemental insulin for only 1 ± 1 day ($P < 0.001$). In fact, supplemental insulin was only required by those EFP patients who had failed the EFP and were crossed over to TPN.

Patients who failed the EFP program required more days of analgesia (9 ± 7 versus 3 ± 4 days; $P < 0.04$) and more days of antiemetics (14 ± 10 versus 7 ± 7 days; $P < 0.06$) than did patients who did not fail the EFP.

Abnormalities in Clinical Laboratory Tests. Despite continuous infusions of electrolytes and minerals in the TPN patients and only occasional i.v. supplements in the EFP patients, only two statistically significant differences were observed: TPN patients were less often hypomagnesemic (serum magnesium < 1.5 meq/liter) than EFP patients (6 ± 7 versus 15 ± 7 days; $P < 0.0001$); TPN patients were more often hyperglycemic (plasma glucose > 150 mg/dl) than EFP patients (9 ± 8 versus 2 ± 3 days; $P < 0.0002$). In fact, hyperglycemia was seen only in those EFP patients who failed the feeding program and were started on TPN.

Although the mean serum concentrations of alanine aminotransferase, total bilirubin, and alkaline phosphatase rose to 200–600% of baseline, there were no treatment-related differences.

During the period of the study, there were no observed instances of severe hypoglycemia, hypophosphatemia, hypomagnesemia, or hypernatremia. Hyperkalemia, hyperphosphatemia, and hypercalcemia were more frequent, but not significantly so, in TPN patients (Table 3). However, catheter-related complications were more likely to result in catheter removal in TPN patients (22 lumens in 13 TPN patients and 8 lumens in 3 EFP patients; $P < 0.007$, Fisher’s Exact test).

There were no complications associated with the placement of nasoenteric feeding tubes.

Hematological Recovery. The mean time from BMT to day of WBC count ≥ 1000 cells/µl was 19 ± 9 days in TPN patients and 20 ± 9 days in EFP patients ($P > 0.56$) and to day of absolute neutrophil count ≥ 500 cells/µl was 21 ± 11 and 22 ±
Because all patients had multipurpose central venous catheter(s) and TPN patients had an additional TPN catheter, it was not always possible to assign a complication to a specific catheter (multipurpose versus TPN). Therefore, values because of catheter placement failure were included in the TPN group for the catheter placement failures. The three TPN patients who were crossed over immediately to the EFP represent the number of all catheter-related complications in each treatment group. The patient who was removed from the study because of protocol violations was not included in this analysis.

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**Table 3 Catheter-related complications**

<table>
<thead>
<tr>
<th></th>
<th>TPN</th>
<th>EFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total catheter-patient days</td>
<td>756</td>
<td>883</td>
</tr>
<tr>
<td>Infections (no. of episodes)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bacteremia</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Catheter insertion/exit site</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>11 (8 patients)*</td>
<td>5 (5 patients)*</td>
</tr>
<tr>
<td>Other complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placement</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Mechanical</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>20 (14 patients)</td>
<td>12 (11 patients)</td>
</tr>
<tr>
<td>Catheter removal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients requiring catheter removal and replacement because of catheter complications</td>
<td>13*</td>
<td>3*</td>
</tr>
<tr>
<td>No. of patients not requiring catheter removal</td>
<td>14</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>33</td>
</tr>
</tbody>
</table>

* $P > 0.1$ (x² goodness-of-fit to the Poisson distribution).

**Fig. 3. Kaplan-Meier survival plot. Probability of survival for the 27 TPN and 33 EFP patients.** (The patient who violated the study protocol was not included in this analysis.) Indicated are the censored data points.

8 days for the TPN and EFP groups, respectively ($P > 0.50$). One patient in each treatment group never recovered hematological function and died in aplasia. There was no difference in hematological recovery day in patients who failed the EFP program and those who did not.

**Graft-versus-Host Disease.** During the 28-day study period, four of 27 TPN patients and three of 30 EFP patients developed acute graft-versus-host disease and were treated with high-dose methylprednisolone and cyclosporine (2).

**Length of Hospitalization and Survival.** The mean time from BMT to discharge from the hospital was 36 ± 18 days for TPN patients and 33 ± 15 days for EFP patients ($P > 0.40$). For patients who failed the EFP and those who did not, mean time from BMT to discharge was 48 ± 31 and 30 ± 9 days, respectively ($P < 0.34$).

There were no treatment-related differences in short-term (100 days) or long-term survival ($P > 0.70$; logrank and Generalized Wilcoxon test) (Fig. 3). When adults (age ≥ 19 years) and children (age < 19 years) were evaluated separately for survival, there were no treatment-related differences ($P > 0.45$; logrank and Generalized Wilcoxon test).

In the proportional hazards model, adults were at greater risk of death than were children ($P < 0.05$); allogeneic patients who did not receive prophylactic cyclosporine were at greater risk than were autologous patients or allogeneic patients who received cyclosporine ($P = 0.05$). After adjustment for age and cyclosporine, we found that neither the nutritional treatment ($P > 0.38$) nor a loss of BCM > 10%, from baseline to day 28 ($P > 0.90$), was associated with increased risk of death.

**Cost Analysis.** Charges were classified as those related to the placement of central venous feeding catheters (average $572$/TPN patient; $32/EFP patient; 4 catheters in 4 patients), those related to i.v. nutrients (amino acids, dextrose, trace elements, vitamins, and lipid emulsions; i.v. electrolytes were not included in the cost analysis; $1686$/TPN patient; $337/EFP patient), those related to i.v. infusion devices (tubing, cassettes for infusion pumps, and dressing change kits; infusion pumps were not included in the cost analysis; $311$/TPN patient; $89/EFP patient), and those related to the enteral diet (additional dietary personnel to prepare and deliver special food items, vitamins, commercially prepared nutrient formulas, feeding tubes, feeding pumps, special food items purchased from outside the hospital; the cost of regular patient trays was not included in the analysis; $6$/TPN patient; $681$/EFP patient). The average cost for the 28-day study period was $2575$/TPN patient and $1139$/EFP patient.

**DISCUSSION**

For many years we have used TPN to support the patients undergoing bone marrow transplantation at our institution. This approach was adopted at a time when patients referred for marrow transplantation routinely presented with residual leukemia (even after multiple courses of aggressive antineoplastic therapy) and malnutrition. I.v. nutritional support was considered necessary because the intensive treatment that these patients faced would limit their voluntary p.o. intake and compromise their already poor nutritional status.

Our BMT patient population has changed, however. Now, most patients are in remission and well nourished, and the goal of nutritional support is no longer nutritional repletion but maintenance of nutritional status. In addition to the change in the BMT patient population, improvements have been made in enteral feeding technology and nutritional assessment methodology, making this clinical trial possible.

As we had expected, the patients who participated in this study were well nourished at the time of hospital admission, confirming the descriptions of BMT recipients published by other transplant centers (38, 39).

The nutrient prescription (35 kcal/kg/day; 1.4 g protein/kg/day) was based on the results of an earlier study (40) in which we estimated the energy intake necessary to maintain the nutritional status of BMT recipients. However, this level of intake could not be achieved by the enteral route alone. Patients in both treatment groups complained that their ability to eat was limited because of anorexia, nausea, vomiting, diarrhea and pain, problems commonly occurring in BMT recipients (41–44) and other patients undergoing aggressive antineoplastic therapy (45, 46). Nevertheless, the enteral intake (15 kcal/kg/day; 0.6 g protein/kg/day) of EFP patients was greater than that of TPN patients and much greater than that (1–5 kcal/kg/day; 0 g protein/kg/day) reported by the Seattle BMT unit (6, 47).

We found that with the TPN program (TPN plus ad libitum p.o. diet), the nutrient intake goals were achieved and BCM was preserved. However, on this carbohydrate-rich TPN solution, body fat and ECF were increased. Patients in the enteral feeding program were not able to achieve the same level of...
energy and protein intake as patients in the TPN group and during the 28-day study period, EFP patients lost weight (BCM and FAT + ECS).

Similar results have been reported by other groups conducting clinical trials to determine whether the routine use of TPN in patients undergoing antineoplastic therapy was better than the "best hospital diet." In some studies, no nutritional benefit could be demonstrated in unselected patients (48–50). In other studies, nitrogen balance or serum proteins were better maintained in TPN patients (51, 52). Most studies, however, demonstrated that the use of TPN only resulted in weight gain, particularly in the fat compartment (53–60). Furthermore, the nutritional "benefits" of TPN were only temporary. Patients usually lost weight and lean body mass, and serum protein levels fell when TPN was discontinued (59, 60).

Investigators have suggested that without TPN, hematological recovery after chemotherapy is slower in patients with sarcoma (61) and leukemia (62). However, the results of our study demonstrate that despite the difference in total energy and protein intake, TPN did not shorten the duration of marrow aplasia after BMT. Furthermore, the difference in nutrient intake and the observed changes in body composition did not influence other clinical outcomes (length of hospitalization or survival).

The results of other clinical trials have failed to show a consistent advantage in hematological recovery or survival in the patients supported with TPN (49, 50, 52, 53, 55–57, 63–65). It is particularly noteworthy that in these clinical trials, as already discussed, there were no real nutritional benefits from TPN. Therefore, it is not surprising that no survival advantage could be derived from the indiscriminate use of TPN.

In the only reported trial evaluating TPN in BMT recipients (66), TPN was initiated prior to chemotherapy and total body irradiation and continued through day 28. The control group received no TPN and apparently no specialized enteral feeding program. The energy and protein intakes of TPN patients were comparable to those achieved in our TPN patients; however, the energy (enteral and total) intake in control patients was considerably less than that achieved in our EFP patients. These investigators found that survival and disease-free interval were significantly greater in TPN patients, but not until after day 100. These results imply that TPN acts to potentiate the effects of antineoplastic therapy rather than to support recovery. Similar observations have been made in tumor model systems in animals (67, 68). The results of our study also support this theory. When nutritional treatments were begun after antineoplastic therapy, no survival advantage could be observed in the TPN group. One might argue that routine TPN is indicated only during the period of cytoreductive therapy and may not be required after BMT in most patients who receive individualized enteral feeding programs. This hypothesis requires further testing.

Catheter-related infectious episodes have been reported to occur in 3–8% of patients on TPN (69–71). These low rates have been achieved by careful catheter care and by limiting the use of central venous catheters to infusions of nutrient solutions. Unfortunately in the treatment of BMT and other critically ill patients, central venous catheters cannot always be used exclusively for TPN. Hickman et al. (7) and Colombani et al. (72) have reported that multipurpose catheters do not necessarily increase the risk of TPN-related infections. In our study, the incidence of catheter-related infections was high, but no patient died directly as a result of a catheter infection. Complications during catheter placement and mechanical problems associated with catheter maintenance were also more common in TPN patients. Because of the frequency of catheter-related complications, TPN patients more often required catheter removal and replacement at a time in their course when they are particularly susceptible to catheter placement complications.

The only complication associated with nasoenteric feeding was occasional feeding tube occlusion that required tube replacement. There were no bleeding or infectious complications in this thrombocytopenic, granulocytopenic patient population. Although cases of aspiration and infection in granulocytopenic patients have been reported (73), with the use of soft-weighted feeding tubes and with careful monitoring, tube feeding appears safe even in BMT recipients (74).

Biochemical abnormalities were seen in both treatment groups. The most frequent abnormalities were hyperglycemia (requiring exogenous insulin) in TPN patients and hypomagnesemia in EFP patients. Hypomagnesemia was, in fact, seen in both treatment groups; however TPN patients received much more magnesium than did EFP patients because the standard TPN solution contained 16 mg/liter.

Elevations (2–4 times normal) in tests of liver function have been reported in patients supported with TPN (75, 76), but these abnormalities are usually temporary, even if TPN is not discontinued. In this study, similar changes were noted, but abnormalities in liver function were as frequent in EFP patients as they were in TPN patients, suggesting that factors other than TPN were responsible.

In this study we demonstrated that TPN was effective in preserving body cell mass in critically ill patients recovering from bone marrow transplantation, but TPN was associated with certain complications and costs. Although the enteral feeding program was less effective in maintaining body cell mass, important clinical outcomes such as hematopoietic recovery rate, length of hospitalization, and survival were unaffected. Furthermore, with the use of the enteral program, most of the toxicities and costs due to TPN were avoided. Thus, we have concluded that TPN is not clearly superior to the enteral feeding program and recommend that TPN be reserved for those BMT recipients who fail enteral methods (including nasoenteric tube feeding).

We would caution clinicians about extrapolating the results of this study to BMT recipients younger than 10 years or to patients undergoing other forms of aggressive antineoplastic treatment. In addition, attention to the needs and wishes of individual patients and an expanded food service were required to achieve these results. Finally, patients must be monitored daily to ensure that goals are being met or to introduce alternate methods of nutritional support when the original plan is not working. We found that this type of care was, in fact, cost effective in the patient population we studied, where TPN had been the standard nutritional therapy.

We recommend that future studies of TPN be prospective randomized clinical trials in which TPN is compared to the best methods of enteral support available. Nutritional status should be assessed by objective, accurate methods, and nutritional outcomes should be correlated with clinical outcomes.

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REFERENCES


Nutritional Support of Bone Marrow Transplant Recipients: A Prospective, Randomized Clinical Trial Comparing Total Parenteral Nutrition to an Enteral Feeding Program


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