Nutrition in Hematopoietic Stem Cell Transplantation

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Recent estimates of the annual number of hematopoietic stem cell transplants (HSCTs) performed worldwide exceed 50,000 with the annual rate of increase at 10,000 transplants. Approximately two thirds of transplants are autologous with the source of stem cells derived from the patient. Among allogeneic transplants, 75% are from family members and 25% from unrelated donors. The demographic characteristics of transplantation continually change as the application of this technology is refined through clinical trials. For example, preliminary results from four trials presented at the 1999 American Society of Clinical Oncology meeting as well as a recently published trial from France [1] suggest marginal benefit for autologous transplantation compared to conventional chemotherapy in women with breast cancer, especially metastatic disease. While these trials require full peer review and longer follow-up periods, the wide dissemination of the early results is expected to influence the number of women choosing to undergo transplant for high risk or metastatic breast cancer. Since 45–50% of all autologous transplants in North America are performed for breast cancer, we can expect a possible decline or slowing of the rate of growth for all autologous transplants.

Allogeneic transplant numbers, on the other hand, may rise as more patients with hematologic malignancies gain access to donors and as the age limit for the procedure rises. Historically the percentage of patients eligible for transplant has been <40% because of the lack of a histocompatible family donor. Histocompatibility has been essential to reduce the risk and severity of one of the major compli-
tations of allogeneic transplantation, the T-cell mediated graft-versus-host disease (GVHD). Furthermore, older patients have been considered ineligible because the very high doses of chemotherapy and/or radiotherapy required for ablation of the immune system present an unacceptable risk for early mortality. The median age of onset for chronic myeloid leukemia is 53 years [2] and for myelodysplastic syndromes in the seventh decade of life [3]. HSCT is the primary curative therapy for these diseases and yet the majority of patients are considered too old for the rigors of transplantation. Some of the trends that are changing the characteristics of allogeneic transplantation are:

1. Growth of the pool of potential marrow donors to over 5 million worldwide such that 60% of patients without a family donor can now locate a HLA-matched donor [4]
2. Establishment of cord blood banks and use of cord blood for stem cells where HLA-matching appears less critical to the success of the transplant
3. Ability to perform transplantation for patients without an HLA-matched family or unrelated donor by a number of advances in immunology and technology. One technology harvests a very large number of CD34+ stem cells through peripheral stem cell collection and depletes the collections of all T cells [5]. The ability to infuse 10-fold the number of stem cells overcomes one of the previous limitations of T-cell-depleted bone marrow transplantation, engraftment failure. Another new technique involves induction of anergy to inactivate alloreactive T cells in the donor marrow before transplantation resulting in successful engraftment without significant risk of GVHD [6]
4. Induction of a mixed chimerism (coexistence of host and donor cells) by infusion of donor stem cells after low-dose chemotherapy and/or radiation and post-transplant immunosuppression. The use of less toxic therapy is appropriate for older patients or those who are otherwise not candidates for traditional transplant regimens because of preexisting organ dysfunction. The goal of mixed chimerism in patients with cancer is to induce a graft-versus-tumor effect and ultimately a cure by stepwise infusion of donor lymphocytes [7]
5. Use of polymerase chain reaction (PCR) technology to detect markers for very minimal amounts of disease, identifying additional candidates for transplant at a time when tumor burden is low and chance for long-term cure is greater. PCR technology is also being investigated to determine when to initiate post-transplant immunotherapy to promote a graft-versus-tumor effect

Why are these trends important for the nutrition support clinician to understand? These trends show that transplantation is at the forefront of clinical immunology; the techniques are changing so fast that our nutrition support practice cannot rest on previous experience or past research. A fundamental problem with much of the past nutrition research is the treatment of transplantation as a homogenous process. Many studies combine autologous and allogeneic patients as well as patients with a wide variety of diagnoses for whom the risks and benefits of the procedure are dramatically different. For autologous transplantation the risk of early mortality is now 5% or less, yet the chance of disease relapse is very high for both solid tumors and hematologic malignancies because it relies completely on the antitumor effects of the preparative regimen. In allogeneic transplantation,
The table below outlines the nutrition-related effects of autologous and allogeneic hematopoietic stem cell transplantation (HSCT).

<table>
<thead>
<tr>
<th>Steps in HSCT</th>
<th>Nutrition-related effects autologous HSCT</th>
<th>Nutrition-related effects allogeneic HSCT</th>
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</thead>
<tbody>
<tr>
<td>1 High dose conditioning to</td>
<td>Mucositis, esophageitis, enteritis</td>
<td>Acute and chronic GVHD</td>
</tr>
<tr>
<td>Eradicate tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suppress host immune system (allogeneic)</td>
<td>Anorexia, dysgeusia, hypoguesia, xerostomia</td>
<td>Oral: stomatitis, xerostomia, taste changes</td>
</tr>
<tr>
<td></td>
<td>Liver (and to a lesser extent lung, heart and kidney) failure</td>
<td>Esophagus: strictures, dysphagia</td>
</tr>
<tr>
<td></td>
<td>Metabolic needs altered by infection</td>
<td>Stomach: nausea, vomiting, anorexia</td>
</tr>
<tr>
<td></td>
<td>Loss of lean body mass</td>
<td>Skin and liver: mild and usually not associated with nutritional side effects</td>
</tr>
<tr>
<td>2 Infusion of autologous or histocompatible allogeneic stem cells to</td>
<td>“Pseudo” acute GVHD</td>
<td>Intestine: diarrhea, abdominal cramping, malabsorption, ileus</td>
</tr>
<tr>
<td>Rescue from lethal toxicity of conditioning</td>
<td></td>
<td>Liver: anorexia, malabsorption</td>
</tr>
<tr>
<td>Eliminate host resistance (allogeneic)</td>
<td>Stomach: nausea, vomiting, anorexia</td>
<td>Lung: hypermetabolism</td>
</tr>
<tr>
<td>Eliminate residual tumor via graft-versus-tumor reaction (allogeneic)</td>
<td>Skin and liver: mild and usually not associated with nutritional side effects</td>
<td>Skin: hypermetabolism</td>
</tr>
<tr>
<td>3 Post-grafting</td>
<td>Cyclosporine: Anorexia, renal dysfunction, severe magnesium wasting, hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>immuno-suppression or T-cell depletion to</td>
<td>Tacrolimus: Renal dysfunction, magnesium wasting, glucose intolerance</td>
<td></td>
</tr>
<tr>
<td>Control GVHD</td>
<td>Corticosteroids: Extreme muscle wasting and debilitation, glucose intolerance, hyperlipidemia, hyperphagia, osteoporosis, growth failure</td>
<td></td>
</tr>
<tr>
<td>Establish long-term graft-host tolerance</td>
<td></td>
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</table>

The reverse is true. Early mortality is high as a consequence of GVHD and its complications, ranging from 10 to 40% depending on patient age and donor source [8]. However, the risk of disease relapse is considerably less owing to the graft-versus-tumor effect that occurs when immunocompetent donor cells attack host tumor cells. Relapse after allogeneic transplantation is as low as 10–20% for chronic leukemia and acute myelogenous leukemia in remission, although when performed for advanced acute leukemia relapse is as high as 65–75% [2, 8]. The nutrition-related consequences between allogeneic and autologous HSCT are detailed in Table 1.

The challenge for nutrition research is establishing relevant outcomes that can account for both early and late risk factors as well as the myriad of other variables that influence transplantation success, including age, donor sex and parity, conditioning regimen, GVHD immunoprophylaxis, previous therapies and health status, including nutritional status. Both underweight [9] and overweight [10, 11]
Table 2. Body weight status and outcome in hematopoietic stem cell transplantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient group</th>
<th>Study design</th>
<th>Outcome</th>
</tr>
</thead>
</table>
| Deeg et al. [9] 1995 | Allogeneic and autologous | Survival analysis by weight categories 100 ± 5% of IBW and 10% segments above and below | Significant relative risks:  
  Adults IBW <85% = 2.11  
  IBW 85–95% = 1.26  
  Children IBW 85–95% = 1.96 |
| | Adults (n = 1,662) Children (n = 576) | Multivariate analysis of weight as risk factor controlling for sex, race, age, disease, allogeneic vs. autologous, transplant year, TBI dose, GVHD prophylaxis and incidence | |
| Fleming et al. [10] 1997 | Allogeneic | Matched case-controlled evaluation of survival in patients > and <120% IBW | Survival significantly worse in adults but not children >120% IBW |
| | Adult (n = 242) Children (n = 80) | | |
| Morton et al. [11] 1998 | Unrelated donor allogeneic for CML | Multivariate analysis of weight ≥110% IBW as one risk factor in outcome | Significant hazard ratio:  
  >110% IBW = 1.8  
  (95% CI 1.1, 3.0) |
| | Adult (n = 174) Children (n = 10) | | |

IBW = Ideal body weight; TBI = total body irradiation; GVHD = graft-versus-host disease; CML = chronic myelogenous leukemia.

have been associated with poor outcome (Table 2). Designing studies with nutritionally important questions will only become more complex as transplantation becomes more diverse.

This chapter will briefly review the research to date in several areas: (1) the use of glutamine to reduce transplant-related toxicity; (2) the use of enteral feedings as a more cost-effective and physiologic approach than the historical standard of total parenteral nutrition (TPN), and (3) the role of lipids on immune-related outcomes.

Glutamine

Most preparative regimens used to eradicate the tumor and, in the case of allogeneic transplantation, to overcome host rejection of donor stem cells result in mild to severe oral mucositis, esophagitis, enteritis, and often liver dysfunction. The organs that result in the dose-limiting toxicity of marrow ablative regimens are almost always the gastrointestinal tract or liver as outlined in Table 3 [12]. The extensive gastrointestinal damage is rarely fatal, but is associated with the need for narcotics to control pain, TPN to prevent significant weight loss, antimicrobials to treat infections and/or fevers of unknown origin felt to be derived from gut organisms, and lengthy hospitalization. Hepatic disease, on the other hand,
Table 3. Toxicity of high-dose preparative regimens used in hematopoietic stem cell transplantation

<table>
<thead>
<tr>
<th>Agent</th>
<th>Maximum tolerated dose</th>
<th>Dose-limiting toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marrow-ablative agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body irradiation</td>
<td>10–16 Gy</td>
<td>Gastrointestinal, hepatic, pulmonary</td>
</tr>
<tr>
<td>Busulfan</td>
<td>20 mg/kg</td>
<td>Gastrointestinal, hepatic, pulmonary</td>
</tr>
<tr>
<td>Carmustine</td>
<td>1,200 mg/m²</td>
<td>Pulmonary, hepatic</td>
</tr>
<tr>
<td>Melphalan</td>
<td>200 mg/kg</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>1,135 mg/m²</td>
<td>Central nervous system, gastrointestinal</td>
</tr>
<tr>
<td><strong>Non-marrow-ablative agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>200 mg/kg</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>18–20 g/m²</td>
<td>Renal, bladder</td>
</tr>
<tr>
<td>Etoposide</td>
<td>2,400 mg/m²</td>
<td>Gastrointestinal</td>
</tr>
</tbody>
</table>

Adapted with permission from Bensinger et al. [12].

can be fatal. Hepatic venoocclusive disease (VOD), which presents as a syndrome of fluid weight gain, hyperbilirubinemia and right upper quandrant pain typically in the early post-transplant period but may occur weeks to months later, results from obstruction of hepatic venules and destruction of hepatocytes in zone 3 of the acinus. There are no effective treatments or prophylactic approaches for VOD or for the damage to the gastrointestinal tract, although many agents have been investigated, including pentoxyfylline, anti-TNF antibody, PGE2, and chlorhexidine as well as a variety of anticoagulants and antithrombolytics in VOD. Other agents such as amifostine and lysofylline are under investigation as a means to prevent oxidative damage or to inhibit stress-activated pathways or inflammatory cytokines [13].

Injury to normal host tissue happens in an essentially glutamine-free environment, owing both to the depletion of glutathione stores by high-dose chemoradiotherapy regimens and the dependence on glutamine-free TPN for extended time periods. The use of pharmacologic doses of glutamine has attracted considerable research in HSCT to ameliorate the gut and liver toxicity (Table 4). Moreover, infectious complications may be reduced by improved gut mucosal integrity and immunity as well as lymphocyte and neutrophil function, as has been suggested in other stressed populations.

Zeigler et al. [14] published one of the first randomized glutamine trials (Table 4) that compared glutamine supplemented to standard TPN in allogeneic transplant patients. The significant findings in this widely referenced study in-
### Table 4. Randomized clinical trials of glutamine in hematopoietic stem cell transplantation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Glutamine route, daily dose and length of therapy</th>
<th>Autograft patients</th>
<th>Allograft patients</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziegler et al.</td>
<td>0.57 g/kg i.v. from day 1 post-transplant until oral intake 50% of kcal needs for 3 days</td>
<td>45</td>
<td></td>
<td>Less clinical infection, decreased length of stay and improved nitrogen balance in glutamine-treated patients</td>
<td>Failed to analyze as intent to treat Neither infections nor criteria for discharge objectively defined</td>
</tr>
<tr>
<td>Ziegler et al.</td>
<td>0.57 g/kg i.v. as above</td>
<td>20</td>
<td></td>
<td>Increased T lymphocytes by flow cytometry post-hospitalization in glutamine group, no difference in B lymphocytes, natural killer cells</td>
<td>T lymphocytes characterized weeks after termination of glutamine, no difference in GVHD but at risk for type II error</td>
</tr>
<tr>
<td>Schloerb and Amare</td>
<td>0.57 g/kg i.v. – start unspecified, end when oral intake 50% of kcal needs</td>
<td>14</td>
<td>15</td>
<td>Decreased length of stay in glutamine-treated patients, no difference in objective infection</td>
<td>Failed to analyze as intent to treat Neither infections nor criteria for discharge objectively defined</td>
</tr>
<tr>
<td>Jebb et al.</td>
<td>16 g oral (divided in 4 doses) from day 1 post-transplant until mucositis resolved or discharge</td>
<td>24</td>
<td></td>
<td>No difference in objective or subjective assessment of mucositis, time to engraftment, hospital stay</td>
<td>Matched for intensity of chemotherapy but failed to analyze as intent to treat</td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>4 g/m² oral suspension (divided into 4 doses) from admission until day 28 post-transplant</td>
<td>87</td>
<td>106</td>
<td>Autologous: Fewer days of opiate use, less mouth pain in glutamine group Allogeneic (matched sibling donors): More days of opiate use in glutamine group Allogeneic (unrelated donors): No difference in days of opiate use All patients: No difference in grade 2 acute or chronic GVHD, infections, or day 100 survival (day 28 survival better in glutamine-treated patients)</td>
<td>Large sample size but inexplicable difference in opiate use in allogeneic patients with related and unrelated donors as well as day 28 vs. 100 survival; lack of correlation between opiate and TPN use Relapse rates reported as not different in abstract but no analysis or data provided Future studies need to measure objectively mucositis including characteristics of oral GVHD</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Duration</td>
<td>Outcomes</td>
<td>Notes</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Brown et al.</td>
<td>50 g glycl-L-glutamine i.v. from conditioning until hospital discharge</td>
<td>27</td>
<td>Higher protein C at days 4 and 7, albumin at days 0 and 4 post-transplant in glutamine-treated patients; no difference at days 11, 14 and 18 after transplant. No difference in markers of thrombin generation (thrombin-antithrombin and prothrombin fragment F1 + 2) or plasmin generation (plasmin u2-antiplasmin)</td>
<td>Protein C may be predictive of VOD but no cases observed in this study; future studies need to target patients at high risk of VOD. If glutamine truly preserves hepatic function by maintenance of glutathione levels, future studies need to ensure that relapse is not higher.</td>
<td></td>
</tr>
<tr>
<td>Schloerb and Skikne</td>
<td>30 g oral (divided into 3 doses) or if unable to swallow 0.57 g/kg i.v. – length of therapy not specified</td>
<td>48</td>
<td>No difference in mucositis (graded by chart review), diarrhea, acute GVHD, length of hospitalization, TPN days. Trend of better long-term survival in glutamine-treated patients with hematologic malignancies.</td>
<td>Failed to analyze as intent to treat. Subgroup analysis exposes to type II errors. Diagnoses too diverse to look at survival.</td>
<td></td>
</tr>
</tbody>
</table>

GVHD = Graft-versus-host disease; VOD = venocclusive disease; TPN = total parenteral nutrition.
cluded a shorter length of stay (29 ± 1 vs. 36 ± 2 days), less patients with clinical infections (3 vs. 9) and improved nitrogen balance (−1.4 ± 0.5 vs. −4.2 ± 1.2 g) for the glutamine-treated compared to the control patients. The findings of this study resulted in several other publications that championed additional benefits of glutamine: less cost [15]; improved mood [16], and greater numbers of T lymphocytes [17]. A fundamental problem with this study is the lack of an a priori hypothesis for the purpose of generating a sample size for the primary question. If the primary endpoint were nitrogen balance, then a sample size of 40–45 would be sufficient to detect the difference in nitrogen balance as reported. However, only half this number were included in the nitrogen balance data. If the primary endpoint were infection, then a much larger sample size would be required. Closer scrutiny of the infection outcome reveals that these investigators did not use an objective, reproducible definition for infections, that is, a positive blood or tissue culture. Of the 10 total infections that occurred in the control group, four were bacteremias and three were cellulitis or catheter exit sites that grew organisms in culture, while the remaining three were non-culture-proven pneumonias. The significance (p = 0.047) would likely not be maintained when seven culture-proven infections in the control group are compared to the three in the glutamine-treated patients. The authors also reported a significantly higher rate of positive throat and stool cultures in the control group, predominantly *Candida albicans*. The relevance of these infection outcomes is further limited by the current antimicrobial prophylaxis regimens now used in HSCT. Fungal infections early after transplantation have been virtually eliminated and are a source of significant morbidity and mortality later posttransplant only for patients with GVHD who are profoundly immunosuppressed for an extended length of time. Finally, the data on length of hospitalization are weakened in that the investigators failed to provide objective criteria for discharge and did not analyze data as intent-to-treat (outliers with extended hospital stays were eliminated).

A similarly designed study using the same dose of intravenous glutamine in TPN by Schloerb and Amare [18] purported no difference in infection outcome but an equivalent shorter length of stay (5.8 days) for glutamine-treated patients. Unfortunately, the same statistical flaws plague this smaller, more heterogenous study that included both autologous and allogeneic patients – lack of objective definitions of endpoints and failure to analyze as intent-to-treat (two outliers, both in the glutamine group, were eliminated).

Schloerb and Skikne [19] recently published a larger trial of 66 patients utilizing oral glutamine to test the hypothesis that delivery of glutamine directly to the gut would better support enterocytes and gut-associated lymphoid tissue. This premise had already been tested on the severity of mucositis in several studies with mixed results. Using a dose of 16 g/day in a small study of autologous patients who were randomized in matched pairs according to the chemotherapy regimen in a dose escalation trial, Jebb et al. [20] found no benefit. In a much larger study, which used a smaller dose of glutamine (4 g/m²) but delivered as a
concentrated suspension, Anderson et al. [21] reported that glutamine-treated autologous patients required significantly (p = 0.005) less opiate (5.0 ± 6.2 days) than controls (10.3 ± 9.8 days) for stomatitis pain. Patients receiving allografts who consumed glutamine, however, required significantly more (p = 0.002) days of opiate (23.2 ± 5.7 days) than controls (16.3 ± 8.3 days). The investigators propose that since glutamine inhibits the renal clearance of methotrexate [22], high serum concentration levels of methotrexate given as prophylaxis for GVHD caused the allogeneic patients to experience more mucositis and narcotic need. In the study by Schloerb and Skikne [19] a larger dose of glutamine (30 g/day) was consumed, and when patients could no longer take the oral dose, parenteral glutamine was provided at 0.57 g/kg. Results were reported only for survivors (n = 52) and by three subgroups: allogeneic with hematologic malignancies (n = 12); autologous with hematologic malignancies (n = 19), and autologous with solid tumor (n = 21). While no differences were observed between groups for mucositis, positive blood cultures and diarrhea, this study is critically exposed to type II errors. When the data for patients with hematological malignancies are combined to look at long-term survival (p = 0.0572 in favor of the glutamine-treated patients), the data are weakened by patients with vastly different prognoses based on transplant type and diagnoses.

The fivefold difference in oral glutamine dose chosen by these investigators reflects the controversy over whether glutamine, the principal fuel for most rapidly growing tumors, may stimulate tumor growth. A recent review of in vivo animal data suggests that glutamine in fact may slow tumor growth [23]. The mechanism is not yet elucidated for the dichotomy in clinical outcome – protection of host and enhancement of tumor-kill – when glutamine is given to cancer-bearing animals treated with chemotherapy (methotrexate) or radiation. One hypothesis attributes the different tissue response in host and tumor to the more acidotic environment of the tumor, which blocks the pH-sensitive enzyme oxoprolinase that recycles glutathione, resulting in a decrease in tumor intracellular glutathione levels and an increase in host levels [23]. However, extrapolating these data to humans becomes problematic, as evidenced by the study by Anderson et al. [21] that showed not less but more clinical toxicity when glutamine was used in allogeneic patients receiving methotrexate.

Glutamine has also been studied as a protective agent against hepatic dysfunction after transplantation. Several case studies [24, 25] have reported therapeutic responses to glutamine and vitamin E for VOD. In a prospective study conducted by Brown et al. [26], 34 patients randomized between glycl-L-glutamine and an isonitrogenous mixture of nonessential amino acids showed no difference in thrombin and plasmin generation and statistically significant differences in serum markers of hepatic function, protein C and albumin at several points early after transplantation. Since no patients in this study developed VOD, it is difficult to attribute too much clinical significance to these findings. Albumin levels routinely drop after transplantation owing to gastrointestinal losses, which were
not accounted for in this study. Future studies to test the hypothesis of a protective effect on the liver need to target those patients at high risk to develop clinical VOD.

At this juncture, pharmacologic doses of glutamine in HSCT cannot be routinely recommended until studies demonstrate that reductions in short-term toxicity, such as decreased opiate use in autologous patients [21], do not result in adverse consequences on long-term outcome. Any effect on relapse rates needs to be defined for solid tumors and hematologic malignancies, since the metabolism of tumors in respect to glutamine metabolism may be different. In allogeneic transplantation, the impact of glutamine as a substrate for T lymphocytes needs to be assessed on rates and severity of GVHD. When Ziegler et al. [17] characterized T-cell populations in the peripheral blood of allogeneic patients treated with and without intravenous glutamine several weeks after termination of therapy, higher levels of total T lymphocytes, CD3+, CD4+ and CD8+ T lymphocytes and no difference in rates of GVHD in glutamine-treated patients were observed. However, the sample size (n = 20) was far too small to exclude the possibility that a difference existed. The mix of GVHD immunophrophylaxis received by patients further complicates the ability to interpret any relationship between glutamine and GVHD. In the study by Anderson et al. [21], an alternative explanation for the findings of more opiate use by the allogeneic recipients could be lymphoid activation of oral GVHD.

The timing of glutamine therapy may also be an important variable in host and/or tumor response. Glutamine has been shown to stimulate IL-2 activation of natural killer cell activity [23]. Natural killer cells infused after allogeneic transplantation in mice appear to have an antitumor effect without the risk of induction of GVHD [27]. The beneficial effects of this immunotherapeutic approach are observed when natural killer cells are administered soon after transplantation because later infusion may actually exacerbate GVHD [28]. Certainly in the glutamine studies published to date, timing of doses has varied both at the initiation (either including or excluding the period of high-dose cyoreduction) and cessation of therapy.

It is anticipated that more glutamine trials in HSCT are forthcoming. Let us hope that the primary endpoint is clearly identified and the sample population of sufficient size to minimize type II errors. If a short-term toxicity or a laboratory surrogate is identified as the endpoint, then the sample should be restricted to patients with similar prognosis for relapse and GVHD so that any adverse or beneficial trends might be identified. Timing, dosage and route of therapy are variables that likely need further examination. Ideally, disease-free survival would be examined as an endpoint, but such a study would need to be very large and require a multicenter trial. Glutamine persists as an intriguing pharmacologic nutrient in HSCT owing to its role in tumor, gut, liver and immune cell metabolism.
Patients undergoing HSCT have long been recognized as appropriate candidates for TPN. Over a decade ago, Weisdorf et al. [29] at the University of Minnesota demonstrated improved long-term survival in transplant patients supported with TPN compared to hydration. When analyzed by transplant type, TPN did not result in a survival advantage for autologous patients, but the number of autologous patients enrolled in this study was too small to rule out a type II error. As with other TPN studies, the risk of infection was higher in the patients on TPN. Among allografted patients, 72% of those in the TPN group experienced bacteremia compared to 48% for the control patients and bacteremia occurred sooner (p = 0.001). Lough et al. [30] also reported a higher infection rate in TPN patients (53%) compared to control patients (7%) in a much smaller study enrolling both autograft (n = 12) and allograft (n = 17) recipients. Another adverse effect is the suppression TPN has on appetite and oral intake after transplantation. In a study conducted by Charuhas et al. [31], patients who were still eating poorly at the time they were medically ready for hospital discharge were blindly randomized to TPN or hydration. Patients on TPN resumed adequate oral energy intake six days later than those supported with hydration and electrolyes (p = 0.049), without any apparent adverse effects measured as hospital readmission rate, relapse or survival. Infection risk, appetite suppression, other TPN-related complications and, of course, cost have led a number of investigators to study the feasibility of enteral feeding in HSCT.

Multiple challenges face the clinician in feeding by the enteral route after marrow ablative preparative regimens. In the milieu of life-threatening thrombocytopenia, placement of nasal feeding tubes in highly irritated oral, sinus and esophageal tissues seems risky to many oncologists. Vomiting often results in displacement of tubes and raises concerns about aspiration pneumonia. Endoscopically placed gastrostomies or jejunostomies must be anticipated well in advance to ensure adequate healing prior to transplantation. Patients’ schedules may be unable to accommodate the extra time because of the advanced stage of their disease or, in the case of an unrelated donor, the coordination of the donation. Diarrhea, ileus and/or abdominal pain are common events that may interrupt feeding, even if enteral access is well established.

Once a patient demonstrates a well-functioning white cell and platelet graft and the oral mucosa and gastrointestinal tract have healed, tube feeding is feasible as a transition step from TPN to oral diet or when nutrition support is indicated for late complications. Roberts and Miller [32] at Baylor University have described such an approach in 16 adult patients who had a percutaneous endoscopic gastrostomy placed between 32 and 1,125 days after transplantation (median 104 days). Some of the patients were neutropenic (data were not provided on actual white blood cell count but none were <1.0 × 10⁹/l) and 75% of the patients required platelet transfusions to boost platelets >50,000 × 10⁹/l prior to percuta-
neous endoscopic gastrostomy placement. Only one patient developed an infection at the tube site. Most patients (80%) tolerated isotonic, intact protein formulas delivered as small boluses every 3–4 h. Scheduled antiemetics and antidiarrheals as well as prokinetic agents were successful in treating the gastrointestinal side effects observed.

Prospective trials that have successfully implemented early post-transplant feeding are lacking. Szeluga et al. [33] randomized adults undergoing allogeneic (n = 46) or autologous (n = 15) transplantation to TPN or an enteral feeding program in which patients became eligible for tube feeding if unable to consume a threshold energy level. Seven (or 23% of the patients) in the enteral group were eligible by study criteria for tube placement, and of these three had severe nausea, vomiting and diarrhea and tube feeding was not attempted. Of the remaining four patients, tube feeding was attempted but unsuccessful. We do not know at what day after transplantation the tube placements were attempted. Additionally, half of the patients in the enteral group were supported with intravenous amino acids because of the inability to consume a threshold protein intake, suggesting that full enteral feeding is a formidable goal.

Using the approach of enteral feeding as an adjunct to TPN, Mulder et al. [34] randomized autologous patients with solid tumors to TPN with and without enteral feeding. They reported less diarrhea in the patients who received tube feeding, but poor gastric emptying limited the ability to deliver very much volume. There was a trend toward more bacteremias in the tube-feeding group, which is counter to the hypothesis that enteral feeding helps prevent bacterial translocation.

Two reports of early tube feeding have been published in children. In one study 29 children were offered enteral nutrition; eight refused and received diet counseling only [35]. Despite an enormous potential for selection bias, the diet advice group was compared to the enteral group in terms of nutritional status parameters and clinical outcomes. Minimal value can be placed on these nonrandomized comparisons with small patient numbers, especially given the wide range of diagnoses (15 acute leukemia and myelodysplasia, three solid tumors, 11 nonmalignant disorders) and the failure to identify the types of transplant received. However, some of the observations in the enteral group are worth noting. As with adults, a significant failure rate of tube feeding was reported; seven patients vomited the tube and one failed treatment owing to diarrhea. Of these patients, six were placed on TPN. Diarrhea, overall, did not seem to be a major problem in these patients treated primarily with high-dose cyclophosphamide with either busulfan or total body irradiation. The second study involved only three transplant patients as part of a larger study of children with high-risk cancer undergoing intensive therapy [36]. Two of the three patients required TPN. The study did support the ability to place nasogastric tubes safely in patients with neutropenia and thrombocytopenia.
If any trends can be detected from the published experience to date, early post-transplant tube feeding as the exclusive modality is associated with a high rate of failure with conventional HSCT conditioning regimens. If TPN is instituted, cost savings for nutrition support are obviated [36]. If dual feeding methods are utilized, cost could conceivably be higher. Prospective studies are keenly needed to assess whether other benefits can accrue from partial or low-dose enteral feeding when used in conjunction with TPN as has been observed in surgical and trauma patients. Enteral feedings are no doubt underutilized as a transitional step from TPN to oral feeding. As HSCT expands to include less myeloablative regimens, early post-transplant feedings in undernourished patients should certainly be implemented.

Lipids

Intravenous lipids have long been utilized for energy [37] and the prevention of the rapid onset of essential fatty acid deficiency in HSCT patients [38], but concerns about infection risk, hepatic dysfunction and thrombocytopenia have compelled many oncologists to use lipids conservatively. Lenssen et al. [39] recently demonstrated a moderate dose of LCT-based lipids (25–30% of total energy) compared to minimal doses (6–8% of total energy) as essential fatty acid deficiency prophylaxis did not influence infectious morbidity in a large trial (n = 512) of autograft and allograft patients. The incidence of bacteremia or fungemia was 22% in both groups in the first month after transplantation. Factors known to influence infection, including prophylactic systemic antifungal therapy, hematopoietic growth factors, and intravenous immunoglobulin were accounted for in the randomization scheme. From a clinical point of view, lipids are a necessary component of TPN regimens, especially with the frequent observation of hyperglycemia owing to preexisting diabetes, stress and corticosteroid use. Whether alternate intravenous fat sources could alter the incidence of infection remains to be tested.

The potential for lipids to modulate GVHD by prostaglandin E₂-mediated reductions in cytokines involved in the pathogenesis of GVHD has been an intriguing hypothesis. A recent report described a decrease in GVHD mortality in patients infused with very high doses of LCT-based lipid (80% of total energy) [40], but this was a small trial (n = 60). In the glucose group, 19 of 31 patients (61%) developed GVHD with five deaths attributed to GVHD, while no GVHD-related deaths occurred in the 21 of 29 patients (72%) with GVHD in the lipid group. Since the median day of death due to acute GVHD was day 90 after transplantation and extended to day 210 well beyond the termination of lipid therapy at day 15 after transplantation, how lipid might alter the course of the disease is only speculative. Furthermore, a higher proportion in the lipid group received a known superior GVHD prophylaxis regimen. Mortality at 18 months was not different between the groups, raising the possibility that multiple testing may
have occurred. In the study conducted by Lenssen et al. [39], which used a lower dose of lipid (25–30% of total kcal), no difference in the incidence of moderate to severe GVHD was observed in the allogeneic patients (n = 419) as well as no difference in morality at six months after transplantation. Clearly more studies are needed to identify whether lipids might influence the outcome from GVHD.

Conclusions

In HSCT as conventionally practiced in the last 30 years, nutrition support has been a life-preserving modality. Whether it can be further leveraged by manipulation of nutrients, route of delivery or timing of therapy to improve outcome remains to be proven. Or whether it can influence outcome in the newer variations of HSCT with partially ablative regimens or adjunctive post-transplant immunotherapy also remains to be seen. Nutrition interventions must either target the major causes of failure in HSCT (relapse and GVHD) or assure that these endpoints are not adversely affected to be of any true value. With thousands of long-term HSCT survivors, there is now also opportunity to focus on secondary cancer prevention. Allogeneic transplant recipients experience a significantly higher risk of new solid cancers that increases over time and is greatest among younger patients [41]. Among patients with chronic GVHD, whose incidence is expected to climb with the growth of unrelated donor transplants, there has been a paucity of research in how nutrition might improve outcome or quality of life in this debilitating disease. The complexity of the immune response associated with the cancer, the introduction of a stem cell graft and the extensive use of immunosuppressive drugs makes contributive clinical nutrition research a challenge in HSCT.

References

Nutrition in Hematopoietic Stem Cell Transplantation


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Discussion

Dr. Ottery: There was a very interesting paper presented at ASPEN from your group, done by an epidemiologist about 4 years ago. This goes back to Dr. Bloch’s question about alternative therapy. The researchers had an excellent repository of data because they told all the patients who came in for bone marrow transplant that it was necessary for them to know everything that the patient had been taking in the recent past in terms of alternative complementary types of therapy. One of the things that I suggested at that meeting was that it would be very interesting to follow up those patients. Do you know if that’s been done or published? I think these are probably the best data of this type that are available.

Dr. Lenssen: I’ll have to tell my colleague that. She’s been struggling with that paper for about a year, so I’ll have to tell her to get it done! She’s analyzing the data as we speak.

Dr. Ottery: Another point I’d like to make is that I think in general we should always put feeding tubes in earlier rather than later. If we know that there will be a long period of time when people aren’t eating, it probably makes sense to put in a feeding tube. It would be very interesting to put needle catheter jejunostomies in a randomized prospective way into patients who you think are going to be at high risk, ensuring that everything is healed before the time they are actually going to need it so we don’t run into the problem of track infection that everybody talks about.

Finally, referring to the Italian article you cited [1], where there was a much higher risk of infection in the carbohydrate-based diet than in the very high fat, my guess is that the patients were on these diets for a fairly long time and so may have developed essential fatty acid deficiency. In that patient population I’ve seen several patients who were highly stressed and who were getting a totally fat-free regimen who developed frank essential fatty acid deficiency; also I think it would probably be exacerbating the graft-versus-host component.

Dr. Lenssen: I totally agree with the last comment. I think it’s a bad design to have a glucose control group, and that’s why in our own infection study we chose to give a certain...
amount of lipid, because we knew essential fatty acids were immunosuppressive and could confound our results. So I agree with you, and I think you need to at least provide the essential nutrients.

In relation to early placement of the tube, that is what we tried to do in our tube-feeding studies which we haven’t yet published. We tried to place percutaneous endoscopic gastrosomies (PEGs) before patients received any conditioning. The challenge in this patient population is that you do need about 10 days for the track to heal, and you don’t always have that with a transplant candidate. We also couldn’t do it where we were using unrelated donors, for logistical reasons. Many patients actually come to transplant neutropenic, so that eliminates all the myelodysplastic syndromes and a lot of the acute myelogenous leukemias. So we ended up with maybe only 25% of our pool being eligible. Then of course the first patient had a terrible track infection, so then we just tried to place tubes nasally. However, I would still like to be able to place PEGs and I’m hoping, now that I’m in a pediatric hospital where our programs will be more integrated, that we can identify who’s going to be a transplant candidate almost at the time of diagnosis. We can get the tube placed well before they would ever come to transplant, and have that route available at the time we start conditioning.

Dr. Gianotti: My question is about the administration of glutamine orally. My concern is about the absorption of glutamine in those patients. Has anyone measured the level of glutamine in the blood? With all the damage that you can do to the gut mucosa, I think that glutamine orally may not be well absorbed.

Dr. Lenssen: I don’t think any of the studies did report glutamine levels. I know Ziegler [2] did in his original study because he gave it intravenously. Some investigators will claim that giving glutamine into the upper gastrointestinal (GI) tract will never have an effect because you don’t have enough enzymatic activity occurring there, and that if benefit is to be obtained from glutamine it would have to be given into the lower GI tract. That’s why if we could establish enteral access and a way to deliver glutamine to the lower GI tract, we might be more likely to see benefit from glutamine.

Dr. Nitenberg: It has been shown that intravenous administration of glutamine in critically ill patients can be efficient, with an increase in glutamine concentrations in the blood, so I think it is possibly best to give it by that route in such patients.

Dr. Mason: I run a nutrition support service for my medical center and have done so for the last decade. We have a very active tertiary care oncology service, including a very large marrow transplant program. My experience over the last decade is entirely reflective of the nature of the talks that you and Dr. Ottery gave this morning. I feel entirely frustrated that I do not really know what to do and how to approach these patients, or what really constitutes a good nutritional approach. The literature is so confused that it’s hard to come up with anything definitive. I would like to challenge our colleagues from the National Cancer Institute who are present today to go back and talk to the powers that be at that institution, to put together an advisory panel that can actually come to some consensus as to what should be the research priorities for nutritional intervention in the cancer patient over the coming decade. Our approach to this is so haphazard right now, and what gets done from the research point of view is also so haphazard.

References