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Nutrient Support in Hematopoietic Cell Transplantation

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ABSTRACT. High-dose cytoreduction and hematopoietic stem cell infusion form the basis for treatment of hematologic cancers, defects or failure of hematopoiesis, and some solid tumors. As an antitumor therapy, allogeneic hematopoietic cell transplantation (HCT) is superior to autologous HCT by induction of a graft-*vs*-tumor effect. However, recipients of allografts suffer higher transplant-related mortality owing to graft-*vs*-host disease (GVHD). Nutrition support research must recognize that HCT is a heterogeneous modality whose short and long-term outcomes are affected by transplant type, preparative regimens, diagnosis, disease stage, age, and nutritional status. The field of HCT will diversify further as lower dose cytoreduction and mixed chimerism grafts allow expansion of the technique to older patients and to other diseases. (*Journal of Parenteral and Enteral Nutrition* **25:**219–228, 2001)

Total parenteral nutrition has been a supportive modality since the early years of transplantation, improving long-term survival for allogeneic patients. Its role in autologous HCT has never been established. Nutrients examined for their potential role in modification of therapy-related toxicity, infections, and nutritional morbidity have included glutamine, antioxidants, and lipids. Trials with glutamine have yielded mixed results to date. Before glutamine can be recommended, studies with sufficient power to examine endpoints of GVHD, relapse, and survival are needed. Early peri-transplant enteral tube feeding has been associated with a high rate of failure based on limited published experience. Alternate approaches to enteric access will be required to enable investigations of the potential benefits from early enteral feeding. Transplant centers that are having success with early enteral feedings need to publish their experience to help in the identification of appropriate candidates.

HEMATOPOIETIC CELL TRANSPLANTATION—INCREASING DIVERSITY

The number of patients undergoing hematopoietic cell transplants (HCT) has grown dramatically over the last decade, with an estimated 50,000 transplants performed worldwide annually. There is marked diversity in risk and outcome for HCT that is dependent on the diagnosis, disease stage, patient age, transplant type (autologous, family related allogeneic, unrelated allogeneic), degree of histocompatibility, preparative conditioning regimen, stem cell source (bone marrow, peripheral blood, placental cord blood), and general clinical status. Most recently in allogeneic HCT, the use of low intensity cytoreduction coupled with post-transplant immunosuppression to establish a mixed chimera graft is being explored.[1] The heterogeneity of HCT bears on how we should view past nutrition research and focus future efforts.

The fundamental differences between autologous and allogeneic HCT must be understood when scrutinizing and applying nutrition-related research. Autologous HCT is associated with low transplant-related mortality, 5% or less, but disappointing cure rates. Allogeneic HCT, on the other hand, results in better long-term cure rates because of the graft-*vs*-tumor effect.[2,3] Although immunocompetent donor cells may check the growth or eliminate host tumor cells, they may also induce fatal graft-*vs*-host disease (GVHD).[4] Thus, high transplant-related mortality characterizes allogeneic HCT and limits its success as a superior antitumor strategy.

Much of the past nutrition research is plagued by mixing transplant type, diagnosis, and other variables known to be associated with different short and long-term outcomes. For nutrition research to be relevant, we need to ensure our interventions do not impede, and in fact help contribute to, successful outcome. Specifically, in autologous HCT for malignancies, nutrition interventions that to date have primarily targeted short term outcomes must be shown not to adversely affect disease relapse. For allogeneic HCT, our efforts may be best aimed at mitigating the physiologic effects of GVHD.

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THE ROLE OF TOTAL PARENTERAL NUTRITION (TPN)—WHEN IS IT INDICATED?

Transplant patients were among the first beneficiaries of central venous access and TPN in the early 1970s to offset the significant weight loss associated with the gastrointestinal toxicities of the myeloablative conditioning regimens and GVHD. TPN was relegated to last priority after infusion of antibiotics, blood products, and other IV medications; the need to better nourish patients gave rise to the dual lumen Hickman catheter.[5,6] Despite early intervention with TPN, patients experienced marked negative nitrogen balance and loss of lean body mass,[7–9] consistent with the parenteral feeding experience in other critically ill patients. Cheney et al,[7] using radiolabeled isotopes, demonstrated loss of over 1.6 kg of body cell mass in the first posttransplant month among patients with leukemia undergoing HCT and supported with TPN at 1.6 times basal energy needs and 1.5 g/kg protein. The role of exercise to reduce the loss of muscle was established in a randomized trial comparing no physical therapy to three or five times weekly on biochemical and anthropometric indices of muscle mass.[10] Unfortunately, this experiment to promote an anabolic state did not translate into a routine part of care in our nutrition support regimens, and physical therapy is too often reserved for rehabilitation.

In the 1980s, Weisdorf et al[11] reported the positive benefits of TPN in well-nourished transplant patients, which contrasted with findings in other cancer patients that TPN should be reserved only for malnourished individuals. The estimated 2-year survival by Kaplan–Meier analysis for the patients supported with TPN (n = 71) was 50% (CI = 34% to 66%), compared to 35% (CI = 23% to 47%) for those on hydration (n = 66). When analyzed by transplant type, the survival difference was not significant for autologous patients (16% *vs* 17% for the TPN and hydration groups, respectively); however, the small numbers (n = 32) expose such a subgroup analysis to a type II error. The mechanism of the influence of TPN on mortality is not understood, because TPN in HCT patients, as in other cancer and non-cancer patient populations, is associated with higher infection rates[11,12] and is unable to maintain lean body mass.[7,9] Although a few other small trials failed to confirm the benefit of TPN compared with no nutrition support[12] or an aggressive enteral feeding program,[9] these were not large enough to rule out type II errors given the differences in risk for outcome among the study patients. A large trial has not been replicated in part because of ethical considerations and the diffusion of HCT out of specialty research facilities into hundreds of community-based transplant units.

One approach to the paucity of recent studies in this field has been to establish the characteristics of HCT patients who require TPN. Iestra and colleagues recently applied standard criteria used in cancer patients as indications for TPN to a retrospective cohort of 86 HCT patients treated for acute myelogenous leukemia or lymphoma.[13] The criteria included the following: 1) severe malnutrition at start of therapy (serum albumin <30 g/L or body mass index below 18.5 kg/m^2); 2) prolonged period of minimal oral intake (<10% of estimated energy requirement 3 of 7 days or <50% 5 of 11 days); or 3) severe weight loss during admission (10% of initial weight). Applying these criteria, TPN was indicated in autologous HCT in only 37% and 50% of patients prepared without (n = 16) and with total body irradiation (n = 28), respectively. In allogeneic HCT, in which total body irradiation was used for all patients, TPN was indicated for 58% of patients with HLA-matched donors (n = 30) and 92% of patients with HLA-mismatched donors (n = 12). Actual implementation of TPN, based on clinical policy of 2 days of oral energy intake less than estimated needs and not expected to improve within one week, was twice as high as that indicated by the author's criteria in autologous patients not receiving total body irradiation. Among autologous patients receiving total body irradiation and HLA-matched allogeneic patients, 20% more patients received TPN than indicated and among HLA-mismatched allogeneic patients, 9% fewer patients received TPN than indicated. These data are consistent with previous observations that patients receiving total body irradiation[14] or methotrexate for prevention of GVHD[15] experience more oral toxicity.

In the absence of survival data, these kinds of studies are helpful to guide clinical decision-making as long as cytoreductive regimens and GVHD immunoprophylaxis remain similar. Linking screening criteria to actual clinical outcome would enhance their utility. Unless multi-center trials with well-defined transplant populations (eg, autologous HCT for lymphoma, allogeneic unrelated donor HCT for chronic myelogenous leukemia) are conducted, sample sizes sufficient to determine efficacy of TPN will not be accrued.

Nutritional status and nutritional outcome

Nutritional status as a variable in outcome and its implication for nutrition support intervention deserve further study. For underweight patients, should TPN be initiated more promptly or rehabilitation attempted to a minimum level of repletion before HCT? For overweight patients, should TPN be withheld longer or weight loss attempted before HCT? In the study by Iestra et al,[13] patients with AML and lymphoma conditioned with cyclosphophamide and total body irradiation who avoided TPN by clinical policy had a significantly higher body mass index (27.0 ± 4.5) compared with the body mass index of those requiring TPN (23.9 ± 3.6).

Several studies have described risks for transplant outcome related to body weight status. Morton et al,[16] in a study assessing the association of interferon therapy pretransplant and outcome in unrelated donor transplant for CML (n = 184), reported that the risk for mortality was significantly higher for patients >110% ideal weight as measured by a hazard ratio of 1.8 (CI 1.1, 3.0). Fleming et al[17] described that among patients undergoing allogeneic HCT for a variety of diseases (n = 322), those >120% ideal weight had significantly inferior survival by Kaplan–Meier estimates compared with matched case controls. Sub-

group analysis revealed overweight as a risk factor only for adults with HLA-matched donors (n = 50).[17]

In a large cohort study of 2238 subjects, of whom 95% had hematologic malignancies, Deeg et al[18] demonstrated significantly higher mortality at day 150 post-transplant among underweight adults (<95% ideal weight) and children (85% to 95% ideal weight) compared with all subjects >95% ideal weight. A trend for higher mortality was noted in children <85% ideal weight, but this association was not statistically significant. Likewise, Dickson et al[19] recently described a significant increase in early mortality in underweight (<80% age-adjusted body mass index) but not overweight patients in a multivariate regression analysis of 473 adults undergoing autologous HCT for hematologic malignancies. Long-term mortality associated with the treatment, however, was significantly higher for both underweight and overweight patients in the Dickson study, as measured by a Kaplan–Meier estimate of 5-year non-relapse mortality. There were no significant effects on estimates of 5-year survival or relapse rates in either underweight or overweight patients, which reassured these researchers that chemotherapy dose adjustments in overweight patients was not resulting in underdosing.

It is difficult to synthesize these studies in a meaningful way for clinical practice. However, they do signal the need to consider extremes of body weight status as variables in research study design. Researchers must also continue to pursue the relevance of altered body habitus to outcome in HCT and the role, if any, for pretransplant intervention, especially repletion of underweight patients or better recognition and response to nutritional risk factors at the time of initial diagnosis and treatment. Unfortunately, despite the paucity of research, it has been reported that obese patients are denied transplants because of the concern for the safety and efficacy of chemotherapy dose regimens based on weight.[20]

STRATEGIES TO REDUCE CONDITIONING-RELATED TOXICITIES AND RELIANCE ON TPN

Conventional transplant preparative regimens are the most intensive therapies used in oncology. The dose-limiting toxicity of marrow ablative regimens is almost always associated with the gastrointestinal tract or liver, especially those containing total body irradiation, alkylating agents (cyclophosphamide, busulfan, melphalan, and thiotepa), and etoposide.[21] The disruption of the mucosal barrier and bacterial translocation contribute to the pathogenesis of infection and fevers of unknown origin in the period of neutropenia immediately after cytoreduction. It is difficult to assess directly the integrity of the gastrointestinal tract, so grading of oral mucositis or diarrheal stool volumes have often served as a surrogate for overall toxicity. Rappaport et al[22] proposed the peak mucositis score and days of TPN required as relevant end-points in trials designed to evaluate agents as gut protectants. Both these indices were associated with increased blood infections in a prospective evaluation of autologous (n = 126) and allogeneic (n = 76) graft recipients, although subgroup analysis suggested days of TPN was significantly associated only for autologous patients. Using the Oral Mucositis Assessment Scale, a new grading system to assist with comparative data between transplant centers, Horowitz et al[23] recently described a similar association between mucositis severity and the risk of infection. A few small studies have assessed intestinal permeability with non-metabolized probes, finding an association of altered permeability with a higher infection rate,[24] but, unfortunately, no association with mucositis severity.[25] In other studies, a disassociation has been noted between oral mucositis and fatal veno-occlusive disease (VOD) of the liver, suggesting that oral evaluations may not mirror the severity of visceral regimen-related toxicity.[26]

Over the years, a variety of strategies have been tested to reduce oral and gut toxicity and their infectious sequelae. The earliest attempts involved bowel sterilization, but patients poorly tolerated oral, non-absorbable antimicrobials. Prophylaxis with systemic antifungal and antiviral agents has aided immensely in preventing oral and gut infections, which otherwise delayed healing. Measures currently under examination to protect against mucositis include both topical agents (transforming growth factor beta, the hematopoietic growth factors G-CSF and GM-CSF) and systemic agents (keratinocyte growth factor, interleukin-11, amifostine, and lisofylline).[27] Glutamine also has been investigated as both a topical and systemic agent.

Glutamine and mucosal toxicity

Nutrient manipulation with pharmacologic doses of glutamine has appealed to nutritionists because of its role as the primary oxidative fuel for enterocytes and lymphocytes. HCT occurs in an essentially glutamine-free environment owing to the depletion of glutathione stores by chemoradiotherapy and the dependence on glutamine-free TPN for an extended time. The earliest trial conducted by Zeigler et al[28] in 45 allogeneic patients has been widely referenced to support the positive influence of glutamine-supplemented TPN on infection outcome and hospital length of stay. This randomized, double-blind trial provided IV glutamine 0.57 g/kg, a dose previously determined as metabolically and neurologically safe,[29] from day one post-HCT until oral intake reached 50% of estimated energy needs for three days. Statistical flaws of this study were lack of an *a priori* hypothesis and failure to analyze as intent to treat. Nitrogen balance, which was determined to be superior in the glutamine (-1.4 ± 0.5 g) compared with the control group (-4.2 ± 1.2 g), was calculated on only one-half of the patients; a sample size calculation suggests the entire sample should have been accrued for a difference of 3 g/d. Finally, the investigators did not use an objective, reproducible definition for infections, that is, a positive blood or tissue culture. Of the 10 infections that occurred in the control group, four had bacteremias, three had cellulitis or catheter exit sites that grew organisms in culture, and three had non-culture proven pneumonias. The significance ($p = .047$) would likely not be main-

tained when the seven culture proven infections in the control group are compared with 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 limited by the current antifungal prophylaxis regimens used in HCT that have greatly reduced *C. albican* infections.[30] Schloerb and Amare[31] used the same study design but did not find reductions in infections, although an equivalent shorter length of stay (5.8 days) for glutamine-treated patients was reported. Unfortunately, the same statistical failure to analyze as intent-to-treat plague this smaller, more heterogeneous study that included both autologous and allogeneic patients. Neither of these trials found a benefit in reducing mucositis or TPN days.

Other investigations have tested the hypothesis that delivery of oral glutamine directly to the gut would reduce oral mucositis and better support enterocytes and gut-associated lymphoid tissue. Jebb et al[32] provided a dose of 16 g/d from day 1 post-HCT until mucositis resolved or hospital discharge in autologous patients (n = 24) randomized in matched pairs according to the chemotherapy regimen in a dose escalation trial. They found no benefit for glutamine on objective or subjective assessment of mucositis, time to engraftment, hospital stay, or days of TPN. In a much larger study, Anderson et al[33] delivered a smaller dose of glutamine (4 g/m^2) but as a concentrated suspension from admission until day 28 post-HCT. Glutamine-treated autologous patients (n = 87) required significantly (p = .005) less opioid (5.0 ± 6.2 days) than controls (10.3 ± 9.8 days) for stomatitis pain. Patients receiving histocompatible related allografts who consumed glutamine, however, required significantly more (p = .002) days of opioid (23.2 ± 5.7 days) than controls (16.3 ± 8.3 days). These investigators postulated that mucositis was worsened in the glutamine-treated allogeneic patients receiving methotrexate as GVHD prophylaxis based on experimental models that show glutamine delays renal clearance of methotrexate.[34] However, among unrelated allografts, no difference was observed with days of opioid use in glutamine (20.7 ± 9.9) compared with control (20.4 ± 8.4) patients despite the same administration of methotrexate. There were no differences in the incidence and type of bacterial and fungal infections observed between the groups; viral infections were higher in the placebo group but no information was provided on the distribution of pretransplant viral serologies to evaluate risk between groups. Although the data were not reported, no differences in TPN use between glutamine and placebo groups were observed.

Schloerb et al[35] conducted a second glutamine trial using 30 g/d orally and, when patients could no longer take the oral dose, 0.57 g/kg in TPN. Mucositis as assessed by medical chart review, positive blood cultures, days of TPN, and diarrhea were similar between glutamine and placebo-treated patients but were analyzed only in survivors and in three subgroups: allogeneic with hematologic malignancies (n = 12), autologous with hematologic malignancies (n = 19), and autologous with solid tumor (n = 21). Such analyses violate intent to treat principles and expose the data to type II errors. When the data for patients with hematologic malignancies was combined to look at long-term survival (p = .0572 in favor of the glutamine-treated patients), the data becomes meaningless because of inclusion of patients with vastly different prognosis based on transplant type and diagnoses. Most recently, Dickson et al[36] described lack of benefit on a variety of clinical parameters with 30 g/d of oral glutamine compared with placebo from start of conditioning therapy to discharge or day 28 post-HCT in autologous (n = 34) and allogeneic (n = 24) patients transplanted for hematologic malignancies. Number of days of TPN in the glutamine-treated (12 *vs* 13 for placebo) and length of stay (21 *vs* 19 days) and number of days and highest grade of mucositis and median days and total diarrhea volume were not different.

Glutamine and potential risks—relapse and GVHD

The five-fold difference in oral glutamine dose chosen by investigators underlies the controversy over whether glutamine, as the principal fuel for most rapidly growing tumors, may stimulate tumor growth. A recent review of *in vivo* animal data suggests glutamine in fact may slow tumor growth.[37] Why the host is protected and the tumor is killed when glutamine is given to cancer-bearing animals treated with chemotherapy (methotrexate) or radiation is unknown. One hypothesis suggests the more acidotic environment of the tumor blocks the pH sensitive enzyme oxoprolinase that recycles glutathione, decreasing tumor intracellular glutathione levels and increasing levels in the host.[37] However, extrapolating these data to humans becomes problematic, as evidenced by the study by Anderson et al[33] in which more, not less, clinical toxicity occurred when glutamine was used in allogeneic patients given methotrexate. In the glutamine studies in HCT to date, relapse rates have been seldom reported.[32,36] Dickson et al[36] found actuarial estimates of 2-year survival and relapse rates similar between glutamine and placebo-treated patients; however, the numbers are small given the inclusion of both autologous and allogeneic patients.

In allogeneic HCT, the impact of glutamine needs to be assessed on rates and severity of GVHD. In theory, glutamine may be beneficial by lowering the inflammatory response of cytoreduction or infections, or it might be harmful by assisting in the activation of T-lymphocytes. In the study by Anderson et al,[33] the authors postulated an alternative explanation for the findings of more opioid use by the allogeneic recipients receiving glutamine as possible lymphoid activation of oral GVHD. Zeigler et al[38] characterized T-cell populations in the peripheral blood of allogeneic patients treated with and without IV glutamine several weeks after termination of therapy, observing higher levels of total lymphocytes, CD3+, CD4+ and CD8+ T-lymphocytes and no difference in CD16+ (natural killer cells), B-lymphocytes, or rates of GVHD in glutamine-treated patients. The mix of GVHD immunoprophylaxis (n = 11 T-cell depleted, n = 6 methotrexate, 3 = no prophy-

TABLE I
Summary of randomized glutamine trials in hematopoietic cell transplantation

Study	No. of autograft patients	No. of allograft patients	Conditioning regimen (no. patients)	Mucositis	Days of TPN	Infection	GVHD	Relapse	Long-term survival
			IV Glutamine						
Zeigler, 1992[28]		45	Cy/TBI/ARA-C (40) Bu/Cy (3) Cy/VP-16/BCNU (2)	ND	ND	+ (see text)	ND	?	?
Schloerb, 1993[31]	14	15	Cy/TBI/ARA-C (26) Bu/Cy (3)	ND	ND	ND	?	?	?
			Oral Glutamine						
Jebb, 1995[32]	24		BCNU/VP-16/melphalan (24)	ND	ND	?	Not applicable	ND at 6 months	?
Anderson, 1998[33]	87	55 sibling 51 URD	Only TBI specified (54 auto, 45 sibling, 42 URD)	+ auto □ sibling ND URD	ND	ND	ND	?	ND[1]
Schloerb, 1999[35]	48	18	Cy + TBI or Bu (19) Cy/VP-16/BCNU (19) Cy/thiotepa (23) Unknown (3)	ND	ND	ND	ND	?	ND[2]
Coughlin Dickson, 2000[36]	34	24	Only TBI specified (33 auto, 23 allo)	ND	ND	?	?	ND	ND

[1]Day 28 survival significantly better for glutamine group but no difference at day 100.
[2]Nonsignificant positive trend for autograft and allograft patients with hematologic malignancy.
Abbreviations: Cy, cyclophosphamide; Bu, busulfan; VP-16, etoposide; ARA-C, cytosine arabinoside; TBI, total body irradiation; BCNU, carmustine; URD, unrelated donor; ND, no difference between glutamine and placebo.
+ = benefit of glutamine over placebo.
□ = benefit of placebo control over glutamine.
? = not reported.

laxis) likely renders such an analysis invalid because GVHD prophylaxis is known to influence the time and pattern of lymphocyte recovery.[39] The sample size was too small to exclude the possibility a difference existed in GVHD rates.

The timing of glutamine therapy may also be an important variable in host or tumor response. Glutamine has been shown to stimulate IL-2 activation of natural killer cell activity.[37] Experimental infusion of natural killer cells early after allogeneic HCT have an antitumor effect,[40] but when infused later may exacerbate GVHD.[41] Similarly, there may be "windows" when glutamine is either indicated or contraindicated. 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 cytoreduction) and cessation of therapy.

Pharmacologic doses of glutamine in HCT cannot be routinely recommended based on the published data (Table I for summary) and until studies demonstrate that reductions in short-term toxicity, such as decreased opioid use in autologous patients,[33] 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, because the metabolism of tumors in respect to glutamine metabolism may be different. 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, any ongoing and future glutamine trials will have sufficient power to examine end-points of relapse and survival. Powell-Tuck et al,[42] who reported a trend toward improved survival in a subset of patients with hematologic malignancies (n = 62; HCT treatment not specified) as part of a larger glutamine study, suggest such a trial would need over 160 patients. The future of glutamine may also be dependent on how other gut protective agents fare, as some of these agents such as interleukin-11[43] and keratinocyte growth factor[44] have been shown experimentally to reduce GVHD while preserving the graft-*vs*-tumor effect.

Glutamine, vitamin E, and liver disease

Glutamine has also been studied as a protective agent against hepatic dysfunction posttransplant. Several case studies[45,46] have reported therapeutic responses to glutamine and vitamin E for VOD. A preliminary report on the prevention of VOD using vitamin E (400 IU/d < 25 kg, 1000 IU/d > 25 kg) with and without glutathione (100 mg/d <25 kg and 150 mg/d >25 kg) in 43 children receiving transplants for acute leukemia with total body irradiation or busulfan-based regimens suggests an incidence of <15% of mild disease only,[47] which compares with an incidence of 25% after HCT, over a third of these fatal.[27] In a prospective study conducted by Brown et al,[48] 34 patients randomized between glycl-L-glutamine and an isonitrogenous mixture of non-essential amino acids showed no difference in thrombin and plasmin gener-

ation and statistically significant differences in serum markers of hepatic function, protein C, and albumin at several points early post-HCT. Because no patients in this study developed VOD, it is difficult to attribute too much clinical significance to these findings. Albumin levels routinely drop posttransplant owing to gastrointestinal losses, which were not accounted for in this study. Future studies to test the hypothesis of a protective effect of glutamine or glutathione with vitamin E on the liver are needed, targeting those patients at highest risk to develop clinical VOD. An animal model of VOD has been developed, and recent studies suggest that both pre- and posttoxin exposure to glutathione improves outcome.[49,50] As with glutamine, the risk of pretransplant glutathione therapy is that of protecting tumor cells from the desired effects of high-dose chemotherapy.

Antioxidants

Other nutrients with "protective" antioxidant properties are depleted posttransplant, including vitamin E and β-carotene.[51,52] Two reports describe the inhibition of lipoperoxidation in HCT by administration of high doses of vitamin C (0.45 to 25 g), vitamin E (800–1000 IU), and in one study β-carotene (45 mg) before the preparative regimen.[53,54] It is critically important that trials of antioxidant intervention in patients with tumors such as leukemia, which respond so well to the oxidative-damage of radiation and alkylating agents, examine the end-points of relapse and survival. Short-term reduction in morbidity is not a benefit if long-term outcome is adversely affected by reversing the depletion of antioxidant status. Investigators at Memorial Sloan Kettering Cancer Center have recently reported that in HL-60 human leukemia cells, vitamin C is protective against oxidative damage in a glutathione-depleted model.[55] The "safe" antioxidant vitamin E, when supplemented at normal levels, has also been demonstrated to interfere with the apoptotic death of tumor cells in mice with brain tumors.[56]

Even short-term morbidity may be variable depending on the pretransplant iron status of the patient. Patients with high iron loads as a result of transfusions are at risk for posttransplant liver dysfunction[57] and may respond to vitamin C by generation of more reactive oxygen species via the Fenton and Haber-Weiss reactions.[58,59]

THE ROLE OF ENTERAL FEEDINGS—ARE THEY FEASIBLE?

Infection risk,[11,12] appetite suppression and delayed refeeding post-HCT,[60] and the hepatobiliary complications[61] associated with the provision of TPN in HCT and cost have led a number of investigators to study the feasibility of enteral feeding in HCT. The potential to modulate the inflammatory response with enteral stimulation alone as has been demonstrated in trauma patients is as compelling a hypothesis as glutamine. The challenges of establishing a safe enteral route after marrow ablative preparative regimens are formidable; bleeding, aspiration pneumonia, and sinusitis are viable concerns for many oncologists. Endoscopically placed gastrostomies or jejunostomies must be anticipated well in advance to ensure adequate healing before transplant, a possible preclusion for patients with advanced disease or unrelated donors. Diarrhea, ileus, or abdominal pain are common events that may interrupt feeding, even if enteral access is well established.

Once a well-functioning white cell and platelet graft is established and oral and gastrointestinal tissues 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 et al[62] have described their experience with such an approach in 16 adult patients who had a percutaneous endoscopic gastrostomy (PEG) placed between 32 and 1125 days posttransplant (median 104 days). Some of the patients were neutropenic (data were not provided on actual white blood count but none were $<1000/mm^3$), and 75% of the patients required platelet transfusions to boost platelets $>50{,}000/mm^3$ before PEG placement. Only one patient developed an infection at the tube site. The majority of the patients tolerated isotonic, intact protein formulas, which were delivered as small boluses every 3 to 4 hours. Scheduled antiemetics, antidiarrheals, and prokinetic agents ameliorated any gastrointestinal side effects according to the authors.

Prospective trials that have successfully implemented early post-HCT enteral feeding are lacking. Szeluga et al[9] randomized adults undergoing allogeneic (n = 46) or autologous (n = 15) HCT 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. Half of the patients in the enteral group were unable to consume a threshold protein intake and were supported with IV amino acids.

Using enteral feeding as an adjunct to TPN, Mulder et al[63] randomized autologous patients with solid tumors to TPN with and without enteral feeding. The patients who received tube feeding had less diarrhea, but poor gastric emptying limited the ability to deliver very much volume. There was a trend toward more bacteremias in the group receiving tube feeding; counter to the hypothesis that enteral feeding helps promote gastrointestinal immunity and lessen bacterial translocation.

Three reports of early tube feeding have been published in children. In one study, children with acute leukemia and myelodysplasia (n = 15), solid tumors (n = 3), or non-malignant disorders (n = 11) were offered enteral nutrition; eight refused and received diet counseling only.[64] Data on the transplant type was not provided. Despite an enormous potential for selection bias, nutritional status parameters and clinical outcomes were compared between the diet advice group and the enteral group. Limited value can be placed on non-randomized comparisons with small patient numbers with a wide range of diagnoses; how-

ever, some 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. The second study involved only three transplant patients as part of a larger study of children with high-risk cancer undergoing intensive therapy.[65] Two of the three patients required TPN. The study did support the ability to place nasogastric tubes safely in patients with neutropenia and thrombocytopenia. The third study also reported experience with a subset of HCT patients (n = 5) among 32 children with cancer who received enteral feeding via PEG.[66] One child developed a local infection, all required TPN on one or more occasion.

Early enteral feeding trial in allogeneic patients

At the Fred Hutchinson Cancer Research Center, we attempted to assess the safety of establishing enteral access before the myeloablative regimen and the efficacy of enteral feeding during the early peri-transplant period in allogeneic patients. For enteral access an endoscopically placed percutaneous gastrostomy with a jejunal extension (PEJ) was selected because it would circumvent complications associated with oral mucositis and esophagitis and be available for long-term use. Patients with related donors, neutrophil count $>$ 1000/mm^3, platelet count $>$ 50,000/mm^3, and $<$125% of ideal body weight were eligible. The study was expanded to include naso-jejunal placement allowing inclusion of unrelated donors. Evaluation of safety included complications of tube placement, infection at the tube site in patients with PEJ, unilateral sinusitis in patients with naso-jejunal tubes, and radiographic pneumonia (focal pulmonary infiltrates) as a representation of aspiration. A peptide-based, isotonic formula was started when oral intake fell below basal needs. Enteral feeding was considered successful if at least 20% of estimated energy needs could be delivered by tube the first month post-HCT (ie, the threshold level to warrant further research).

The goal was to enroll 15 patients; eight patients were ultimately enrolled in the study. One adult patient had a PEJ placed, 5 adults had naso-jejunal tubes placed, and 2 (1 child, 1 adult) with preexisting permanent feeding tubes participated. The patient with the PEJ had the tube pulled 10 days after placement for fever and site infection, which also delayed transplant. Among the five adult patients with naso-jejunal tubes placed, four were ineligible for and the fifth refused a PEJ. One patient's tube was pulled before conditioning because the transplant was delayed; a second tube could not be placed. Three patients, despite scheduled antiemetics, vomited their tubes after chemotherapy and refused replacement. The fifth patient requested removal of the tube during irradiation. A 5-year-old with a surgically placed gastrostomy received a pediatric peptide formula through his conditioning regimen during which he experienced daily emesis. On the day of his unrelated donor transplant, the tube feeding was stopped because of multiple episodes of emesis and diarrhea in excess of 25 ml/kg. Enteral feeds were resumed on day 16 posttransplant, but he failed the efficacy endpoint for early enteral feeding because for only 17% of the study period did he receive the 20% of energy by the enteral route. An adult patient who was status post antrectomy and jejunostomy placement underwent a second HCT and had enteral feeding initiated day 1 post-HCT. By day 6 she developed a clinical and radiographic picture suggesting typhlitis; feedings were stopped, and on day 7 her tube fell out.

Recommendations for future study

If enteral access could be established and feeding tolerated at a threshold level, a variety of hypotheses could then be tested with early enteral feeding, including the influence of enteral nutrition on gastrointestinal and hepatobiliary function and recovery postcytoreduction, and on the incidence and types of blood infections. It would also provide the ability to manipulate nutrient substrates, deliver gut protectants to the intestines, and, if absorption was sufficient, provide oral forms of expensive IV medications.

Based on the limited experience available for review, early post-HCT enteral tube feeding is associated with a high rate of failure with conventional conditioning regimens.[9,62–66] In our own experience, we also were unsuccessful as described here in a small number of patients. In order to conduct prospective studies assessing what benefits might accrue from enteral feeding, alternate approaches to access need to be considered. For PEJ placement, centers with better-risk patients who have HLA-matched donors may be able to demonstrate safety of this approach before it is expanded to patients with unrelated donors. Placement should also be considered during and shortly after initial disease treatment, which will require increased collaboration between general oncologists, gastroenterologists, and transplant physicians. For naso-jejunal placement, a tube that is resistant to regurgitation, as is available in Europe (Flo-care, Nutricia, Bornem, Belgium), may stay in place more successfully.[67] Transplant centers that are having success with early enteral feedings need to publish their experience to help in the identification of appropriate candidates. From a cost perspective, if TPN is instituted, as has been reported to date for the majority of enterally fed patients, cost savings for nutrition support may be obviated. If dual feeding methods are utilized, cost could conceivably be higher. As HCT expands to include less myeloablative regimens, enteral feedings in undernourished patients is certainly an alternative to TPN.

LIPIDS AND IMMUNOLOGICAL FUNCTION IN HCT

Lipids and their role in immune modulation after HCT have not received as much scrutiny as they deserve. Initial investigations focused on the use of IV lipid as an energy source[68] and as prophylaxis against the rapid onset of biochemical essential fatty acid deficiency.[69,70] Many oncologists, because of concerns about infection risk, hepatic and pulmonary dysfunction, and thrombocytopenia have often used lipid emulsions conservatively. In a retrospective cohort analysis

of IV lipid use and infection at the Fred Hutchinson Cancer Research Center, risk for bacteremia and fungemia increased with IV lipid dose,[71] compelling us to conduct a randomized study with linoleic acid-based lipid emulsion on rates of blood infections.[72] Patients (n = 512; 82% allogeneic) were randomized by a scheme that balanced multiple variables (prophylactic systemic antifungal therapy, hematopoietic growth factors, IV immunoglobulin, corticosteroids as GVHD prophylaxis, pentoxifylline, and total body irradiation) to standard (25% to 30% of total energy) or low (6% to 8% of total energy) dose lipid. The goal was to compare a dose of lipid commonly recommended for critically ill patients with the lowest dose felt to prevent essential fatty acid deficiency in HCT patients[70] because essential fatty acid deficiency also leads to immune anomalies and experimental bacterial translocation.[73] The incidence of bacteremia and fungemia was 22% in both groups in the first month posttransplant; the mean time of onset of first blood infection was not different between groups, 13.3 ± 8.7 days in the standard *vs* 14.1 ± 7.6 days in low lipid group. Among patients who experienced a blood infection, the effect of lipid treatment on the risk of another infection was not significantly different. Whether medium chain triglyceride solutions might result in a reduction in infection rate remains to be investigated.

The hypothesis that lipids might favorably modulate GVHD by blunting cytokine production via prostaglandin E2-mediated pathways has intrigued several investigators. In the trial of lipids and blood infections, a secondary endpoint was the incidence of GVHD in allograft recipients, which occurred as grades II–IV in 77% of patients on standard and 75% of patients on low dose lipid.[72] At this moderate lipid dose, no association (p = .30) was found between lipid group and time to grades II–IV GVHD censored for 80 days posttransplant, death, relapse, and treatment failure. In a recent trial that compared very high doses of linoleic-acid based lipid (80% of total energy) to lipid-free, 100% glucose-based TPN in 66 allograft patients, a decrease in acute GVHD mortality (5 *vs* 0) was observed in the lipid group.[74] No difference, however, was observed for incidence of acute GVHD grades I–II (55% in both groups) or III-IV (6% in lipid *vs* 17% in glucose group) or median day of onset GVHD. Statistical concerns arise from the small sample size for the endpoint of interest and the multiple testing risk and the difference in GVHD prophylaxis between the groups. Although not different statistically, a higher percentage in the lipid group received a combination regimen of cyclosporine and methotrexate (known to be superior to cyclosporine alone). From these studies, along with experimental models of GVHD in which dietary fish oil supplementation failed to modify disease activity,[75] it is unclear if long chain fatty acids have any role in modulating the severity of GVHD.

CONCLUSIONS

On one level, it seems we have made little progress in the nutrient support of patients undergoing conventional HCT over the last 25 years. We are still asking who needs to be supported with TPN, for how long, and with what substrates. Looking from the next level, we can see ourselves in a better position to answer some of these questions now because of the large number of patients undergoing treatment. At the highest level, we need to recognize that our research in nutrition support interventions must not only demonstrate clear benefit but also confer no harm in the direction of HCT failure—relapse and GVHD. We have opportunities to explore further enteral feeding, alternate lipid sources, and the timing of antioxidant repletion. Trials of antioxidants that might behave in a more pro-oxidant manner in this setting will need to be well designed to answer safety questions. Despite the large numbers of HCT patients, the diverse nature of the treatment requires us to define our study populations well, likely necessitating collaborations between facilities to gain sufficient power with a given treatment or diagnosis. With the anticipated growth of unrelated donor and non-myeloablative allogeneic HCT, we will also have opportunities to study how nutrient support and adjunctive anabolic therapies might improve outcome or quality of life in chronic GVHD. We urge investigators working in this field to study only homogenous patient populations receiving identical conditioning therapies, GVHD prophylaxis, and infection prophylaxis. Otherwise, evidence for the efficacy of nutritional approaches will be obscured by widely divergent risk factors that bear on morbidity and outcome post-HCT.

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