Controlled Clinical Trials of Nutritional Intervention as an Adjunct to Chemotherapy, with a Comment on Nutrition and Drug Resistance


Abstract

Nutritional intervention in the cancer patient [e.g., total parenteral nutrition (TPN)] might improve durable survival because of increased tolerance to aggressive tumor therapy. To determine whether this assumption is correct, 42 patients with diffuse histiocytic lymphoma were induced with prednisone, high-dose methotrexate, Adriamycin, cyclophosphamide, and VP-16 (ProMACE). Nitrogen mustard-vincristine-procarbazine-prednisone (MOPP) consolidation was then used, followed by late intensification with ProMACE. Patients were selected randomly to receive adjuvant TPN or a standard diet during ProMACE-MOPP treatment. While TPN patients had a greater median weight gain than did control patients, lean body mass and degree of myelosuppression did not differ between the 2 groups; drug tolerance was not improved as a consequence of TPN. There was no significant difference in tumor response or survival between TPN and control patients, whether or not the patients were initially malnourished. In a second trial, 32 young patients with metastatic or other poor-prognosis sarcomas were randomly allocated to receive TPN or a standard diet as an adjunct to one very intensive course of combination chemotherapy or chemotherapy plus total body irradiation; autologous marrow transplantation was used with certain regimens. TPN patients experienced a greater weight gain than did controls but remained in a negative nitrogen balance. Response rates and median durable survival did not differ between the two groups. In both trials, the maximum nutritional support permitted by currently available technology was offered. Thus, the limiting factor may not be nutritional status but rather the intrinsic biology of the tumors and the limitations of their response to current therapy.

In in vitro studies of the possible influence of nutrition on cancer treatment, we have compared sublines of P388 murine leukemia cells which are sensitive or resistant to Adriamycin. The difference in drug sensitivity correlated with differences in lipid composition, with more intracellular lipid, and with greater membrane rigidity in the resistant cells. Resistant cells have a relatively poor transport of drug into the cell; moreover, intracellular Adriamycin is sequestered in lipid depots away from DNA. These results suggest one possible relationship between nutritional phenomena and drug sensitivity.

Introduction

The most compelling question to be posed in studies of nutritional intervention in the patient with cancer is whether such intervention will yield a significantly improved durable survival. Controlled clinical trials of TPN[2] may serve as a paradigm in addressing this question (1). It is evident that certain basic assumptions underlie treatment regimens which use TPN (2). The tumor and/or its therapy, whether surgery, chemotherapy, or radiotherapy, must induce some variant of malnutrition. Also, the malnutrition must in fact be reversible by a manipulation such as TPN. Moreover, it should be demonstrable that, if nutritional defects are corrected, tolerance to cancer therapy will improve; i.e., either the dose or dose rate (or both) of the cancer treatment can be increased. To establish the ultimate utility of TPN (or any supportive care maneuver), this increase in the maximum tolerable dose or dose rate of the tumor therapy should promote an increased tumor response with respect to an increased remission rate and/or a longer remission duration. Finally, this improved tumor response should yield a significant improvement in durable survival. In essence, these assumptions reflect the notion that there are at least some tumors, at some point in their natural histories, that demonstrate a relatively linear dose-response relationship. One of the reasons for failing to achieve effective tumoricidal doses or dose rates on this linear plot would be failure to correct a nutritional deficiency (3). It is this notion which trials of nutritional intervention in cancer patients must address directly, as in all trials of supportive care maneuvers (9). However, the failure to achieve long-term tumor control with sophisticated supportive care technologies is more likely to be due to the lack of an effective tumoricidal treatment than to our inability to provide effective supportive care (10). Moreover, it must be noted that, in some studies involving animal tumor models, a change in nutritional status has favored the tumor rather than the host (15). In this regard, Goldie and Coldman (8) have proposed that drug resistance may relate to the spontaneous rate of somatic mutation within tumor cells. If an improvement in nutrition were to enhance the proliferative rate of the tumor, this increased rate might reflect an increase in the rate at which somatic mutation occurs, favoring drug resistance.

Thus, meaningful clinical trials of TPN in young cancer patients require that the tumor be responsive (i.e., at the maximum achievable dose and/or dose rate, a significant number of tumor regressions must ensue); moreover, this dose or dose rate must not be achievable unless nutritional defects are corrected. In essence, the responsive tumor is not permitted to respond mainly because of the nutritional status of the host (4). It is evident that controlled clinical trials of TPN in young cancer patients must therefore be stratified with respect to the type of tumor being studied, since tumors are differentially responsive to various treatments. Tumor stage and other

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2 The abbreviations used are: TPN, total parenteral nutrition; NCI, National Cancer Institute; MOPP, nitrogen mustard-vincristine-procarbazine-prednisone; ProMACE, prednisone-methotrexate-Adriamycin-cyclophosphamide-VP-16; DTIC, dimethyl-triazeno imidazole carboxamide.
known prognostic variables must also be stratified. Ideally, such trials should involve one potentially responsive tumor at one point in its natural history with all patients comparably staged and otherwise comparable for known prognostic variables. Other known variables which affect treatment tolerance, response, and survival, e.g., infection, antecedent weight loss, and gastrointestinal toxicity, might also be stratified. Finally, one must consider the effect of other supportive care modalities, such as antibiotics, laminar flow isolation, bone marrow transplantation, and granulocyte transfusion (9, 10); each one of these supportive care modalities, because it may improve the tolerance to therapy in any given patient, competes with TPN and therefore potentially clouds our understanding of the utility of TPN. Finally, there are assuredly unknown prognostic variables as well as those that can be identified. Since the impact of TPN on ultimate survival may be modest, it is evident that this modest effect will be demonstrated unequivocally only in prospectively randomized studies. Patients in both arms of such studies would be treated identically except for the one variable of nutritional intervention; dose and/or dose rate would then be escalated as a direct consequence of objectively improved tolerance. However, cancer in the younger end of the age spectrum is infrequent, and to accrue the necessarily large numbers of such patients required for a well-designed study will therefore by extremely difficult. It may in fact be impossible to identify a subset of the pediatric cancer population which has a tumor that demonstrates linear dose-response relations with extant therapy and which exists in sufficient numbers to permit the demonstration that this subset has its response compromised by reversible malnutrition. Some idea of the magnitude of the appropriate controlled clinical trial of TPN in pediatric cancer treatment can be obtained through the following reasoning. One might assume that the true success rate with respect to long-term survival in a given pediatric tumor is 50% and that TPN may improve this survival figure to 70% (on the basis of nutritional intervention permitting a higher dose or dose rate of treatment). To demonstrate this 20% improvement with statistical significance, it is required that there be approximately 100 evaluable patients in each arm of a randomized, prospectively controlled trial (14). If in fact the improvement in median survival is only 10 to 15%, then 200 to 500 evaluable patients would be required in each arm of the study. It is evident that few if any centers, or even cooperative groups, would be able to complete such a trial because of the relative rarity of pediatric cancer and the rapidity with which tumor therapy regimens change.

NCI Trial of TPN in Advanced Stages of Diffuse Lymphomas

Two prospectively randomized clinical trials have been initiated at the NCI designed to assess the role of TPN in cancer treatment. In the design of these trials, we have sought to determine whether patients are initially debilitated, the etiology of this debilitation, whether the debilitation is reversible with TPN, and whether TPN permits an increased dose or dose rate which in turn yields an improved durable survival. The first such clinical trial of TPN undertaken at the NCI involved adult patients with advanced stages of diffuse aggressive non-Hodgkin’s lymphomas (11, 12). Historically, such patients (the majority of whom have diffuse histiocytic lymphoma), treated initially at the NCI with the bleomycin-Adriamycin-cyclophosphamide-vincristine-prednisone, MOPP, or cyclophosphamide-MOPP regimens, experienced a 46% complete remission rate; 38% survived disease free and off therapy at 5 years (6).

For the past 4 years, patients with advanced stages of diffuse non-Hodgkin’s lymphomas have been treated in the Medicine Branch of the NCI with the “ProMACE-MOPP” regimen (5). This study was designed to increase the complete remission rates and, therefore, the long-term survival of patients with aggressive lymphomas by treatment with ProMACE induction therapy (consisting of a new regimen of active drugs), MOPP consolidation therapy with a known effective regimen which does not contain any of the drugs used in the induction regimens, and aggressive late intensification with the initial ProMACE induction regimen. The ProMACE regimen consists of the following agents. On Days 1 and 8 of the cycle, the patients receive i.v. VP-16, 120 mg/sq m; cyclophosphamide, 650 mg/sq m; and Adriamycin, 25 mg/sq m. On Day 14, patients receive i.v. methotrexate, 1.5 g/sq m; 24 hr later, leucovorin rescue is initiated. Prednisone, 60 mg/sq m, is given every day for the first 14 days. A cycle of ProMACE lasted 28 days. Since not all patients respond to chemotherapy at the same rate, the duration of the patient’s induction, consolidation, or late intensification therapy was tailored to the responsiveness of the patient’s particular tumor. Patients who achieved a clinical remission slowly would receive more therapy than those whose rate of response was more rapid. A patient would remain on a given phase of this therapy until the rate of response of his tumor decreased or complete remission was achieved. In addition, patients entering the ProMACE-MOPP trial were randomized to receive either total parenteral nutrition or a standard diet in order to determine the role of hyperalimentation in preventing weight loss, improving nutritional status, permitting increased chemotherapy dosage, and increasing the complete response rate and long-term survival of these patients.

As in earlier NCI trials in the diffuse lymphomas, the majority of patients in this trial (70%) had diffuse histiocytic lymphoma, and about 60% were Stage IV. Analysis of the results of the ProMACE-MOPP regimen indicates that the pathologically documented complete response rate has increased from 46% (bleomycin-Adriamycin-cyclophosphamide-vincristine-prednisone, MOPP, cyclophosphamide-MOPP) to 72%, with the complete response higher in each prognostic category. Moreover, actuarial analyses predict an increase in the number of patients cured of their disease from 38% to approximately 60%.

Twenty-one of 42 patients with advanced diffuse lymphoma were randomly selected to receive adjuvant TPN during the ProMACE-MOPP study. Fifty-six TPN courses were given during the first 14 days of the 28-day ProMACE induction and late-intensification cycles. The other 21 patients were randomly allocated to receive conventional p.o. nutrition. Because of significant marrow suppression, all patients required dose modifications during treatment. One aim of the study was to determine whether patients receiving TPN would be able to tolerate a greater drug dosage and if, as a consequence, the overall tumor response would be enhanced.

TPN patients received an average of 2200 kcal/day and ate an additional 800 kcal/day during therapy. These patients had marked weight gains, whereas conventional-diet patients had stable weights both during induction and late intensification cycles and over the entire course of the therapy. Lean body mass, as indicated by total body potassium, anthropomorphic...
measurements, serum albumin, creatinine:height ratio, total iron-binding capacity, and total lymphocyte count, was not improved in TPN patients as compared to control patients. These results suggest that the weight gained by TPN patients was composed of fat, water, or both. It might be the case that TPN would by some mechanism protect against treatment-induced myelosuppression and in this way improve the tolerance to myelosuppressive treatment. However, the median granulocyte count nadir and the time taken to achieve this nadir were not different between the 2 study arms. Moreover, no differences were noted between the platelet nadir counts or the days at which the nadirs were achieved. Thus, in this trial, TPN did not promote myeloid recovery and on this basis would not have permitted more intensive treatment.

The dose of the chemotherapeutic agents to be administered was decreased only according to predetermined toxicity guidelines. Thus, a comparison of drug dosage in the group receiving TPN and the group receiving conventional p.o. nutrition is a measure of drug tolerance in these patients. In fact, no difference in tolerance of any specific drug or total drug dose occurred when all patients in both groups were compared. Similar comparisons in subgroups of malnourished patients and responding patients also revealed no difference. Moreover, a cycle-by-cycle analysis demonstrated no difference in any phase of therapy. As a group, TPN patients received approximately 88% of the idealized cumulative dose, and the dose at the 25th percentile was approximately 71%. Patients receiving conventional p.o. nutrition were able to receive approximately 84% of the idealized dose, and the 25th percentile dose in the control group was approximately 78%.

Of patients who were malnourished at the inception of the study, those receiving TPN were able to tolerate 86% of the idealized dose, while patients in this category and receiving conventional p.o. nutrition were able to receive 81% of the idealized dose; again, this result was not statistically significant between the 2 arms of the study. Patients receiving TPN who achieved complete remission were able to tolerate 89% of the idealized dose, while patients achieving complete remission who had received conventional p.o. nutrition were able to tolerate approximately 85%. Thus, in this randomized, prospectively controlled trial involving adult patients with diffuse lymphomas, there is no evidence that drug tolerance has been improved as a consequence of TPN. Moreover, there was no significant difference in survival between patients receiving TPN or p.o. nutrition, whether or not the patients were initially malnourished.

**NCI Trial of TPN in Young Patients with Poor-Prognosis Sarcomas**

A second prospectively randomized trial of TPN at the NCI involves young patients with metastatic, recurrent, or in the case of Ewing’s sarcoma) central axis sarcoma (13). The tumors under study include Ewing’s sarcoma, rhabdomyosarcoma, and osteosarcoma. In all of these settings, TPN is administered in conjunction with one very intensive course of chemotherapy or chemotherapy and radiotherapy. Patients randomly allocated to the TPN group receive 40 kcal/kg/day, with nitrogen, 0.3 g/kg ideal weight, as a mixture of 20–25% dextrose and 4.25% Freamine. TPN is administered until p.o. intake is established at greater than 2000 kcal/day. At the time of this report, 14 patients have been randomized to receive TPN and 18 patients to receive conventional p.o. nutrition.

In this study, Ewing’s sarcoma patients are enrolled who have either metastatic disease at presentation or a central axis primary tumor. In both settings, survival has been extremely poor. These patients are initially treated with radiation to all areas of bulk disease and with vincristine, actinomycin D, and cyclophosphamide. If marrow is free of detectable tumor, it is harvested, and cryopreserved. The patient is next treated with a course of total-body irradiation (150 rads) followed by high-dose chemotherapy with vincristine, Adriamycin, cyclophosphamide (45 mg/kg), and DTIC. Autologous marrow transplantation is then carried out (7). The period of observation for the TPN trial consists of the total-body irradiation-high-dose chemotherapy-marrow rescue cycle.

Rhabdomyosarcoma patients entering this TPN study are those with metastatic disease at presentation or with disease recurrence. These patients are treated with cycles of DTIC, Adriamycin, and cyclophosphamide (45 mg/kg); with each successive cycle, the cumulative dose of cyclophosphamide is escalated (from one to 4 consecutive days of treatment). It is during the final cycle, during which patients may also receive autologous marrow transplantation and be isolated within laminar air flow rooms, that TPN is studied.

The osteosarcoma patients in this TPN trial differ from patients with the other 2 tumors in that they have no bulk disease. These are patients who either have presented with metastases or have developed metastases subsequent to diagnosis and the inception of adjuvant therapy. They have had metastatectomy and are free of detectable disease at the time of entry into the TPN trial. One intensive course of chemotherapy is given following metastatectomy, consisting of high-dose methotrexate (with leucovorin), Adriamycin, cyclophosphamide, DTIC, L-phenylalanine mustard, and cis-platinum. Maximum tolerable doses of each of the drugs are administered including 3 days of cyclophosphamide at 45 mg/kg.

Table 1 demonstrates pre- and posttreatment nutritional parameters in the 2 groups of the study. It can be seen that patients receiving TPN had a slightly lower preillness weight than did those in the control group. Mean caloric intake in the TPN group was more than twice that in the control group, and mean intake of nitrogen was almost 6-fold greater amongst TPN patients. Nitrogen balance was much less negative in the TPN group than in the control group, but it is clear that even in the TPN group nitrogen balance was not restored. A least-squares linear regression analysis suggests that a caloric intake of 1875 calories/sq m/day and a nitrogen intake of 10.1 g/sq m/day would be required in this patient group to achieve nitrogen balance, but delivery of these quantities is limited by the necessary amount of fluid. The data in Table 1 demonstrate that there were no significant differences between the 2 treatment groups with respect to serum albumin concentration, total serum proteins, or transferrin concentration before or after the period of nutritional intervention. As in other reported studies of TPN (1–4), there was a significant impact of nutritional intervention on weight, with 75% of the patients in the control arm experiencing a weight loss and 90% of the patients in the TPN group experiencing a weight gain.

In this study of the utility of nutritional intervention in the treatment of resistant sarcomas, the proportion of patients demonstrating partial plus complete responses to the intensive
course of chemo- and radiotherapy and the median long-term survival have not differed between the 2 treatment arms. With respect to short-term survival, patients in the TPN group do appear to demonstrate a small advantage (Chart 1). However, a number of variables potentially confound this analysis, including laminar flow isolation and autologous marrow transplantation, as well as the prognostic implications of the particular but varied tumor types under study and their intrinsic biology and treatment. With this very small data base, it is not possible to determine whether the apparent improvement in short-term survival of TPN patients is in fact a function of TPN or of other variable factors in this group. Importantly, Chart 1 demonstrates that ultimately patients receiving TPN have not had an improved long-term survival as compared with patients in the control arm.

Discussion

The results of these 2 prospectively randomized NCI studies, one in adult patients with diffuse non-Hodgkin's lymphoma and the second in young patients with poor-prognosis sarcomas (still preliminary), fail to demonstrate that nutritional intervention in the form of total parenteral nutrition has permitted a greater dose or dose rate of primary tumor treatment to be delivered with the consequence of an improved tumor response and longer median survival. In both studies, patients receiving TPN did gain more weight than patients receiving conventional p.o. nutrition. However, despite the fact that we administered the maximum nutritional support permitted by currently available technology, nitrogen balance was never entirely restored, and there were no significant differences in total serum proteins, albumin, transferrin, or recovery from myelosuppression between control and hyperalimented patients. While idealized nutrition was not achieved with TPN, it does seem likely that a sufficient nutritional improvement was obtained, such that any significant impact on tumor outcome would have been detected. One may conclude, therefore, that the limiting factor in these 2 trials was not nutritional status but rather the intrinsic biology of the tumors and the limitations of their response to available tumor therapy. This, of course, has been the limitation with other supportive care maneuvers. Supportive care, whatever the modality used, can only permit a given tumor treatment to be delivered. If the tumor treatment is ineffective, or only modestly effective, there will be no effect of supportive care on ultimate survival. If, however, TPN does act modestly in improving patient tolerance to a modestly effective treatment, a very large randomized trial will be necessary to demonstrate this result. In practice, our preliminary data suggest that such a study cannot be achieved among young tumor patients because of insufficient patient accrual. In the final analysis, studies designed to answer the question of whether TPN is a major adjunct to cancer treatment require that TPN candidates be malnourished (and not able to be renourished enterally), that their tumors be potentially responsive, and that they cannot receive an adequate trial of intensive therapy because of the effects of malnutrition. Well-nourished patients and patients for whom there is no effective therapy will receive no benefit from TPN.

In addition to the question of hyperalimentation and its impact on the delivery of conventional cancer treatment, there is the question of specific nutritional manipulations as they may relate to drug resistance and sensitivity. The latter area of nutritional intervention may in fact be of far greater importance than the former, and in the remainder of this discussion we shall consider one example of a specific nutritional phenomenon within tumor cells and its relationship to drug sensitivity.

We have studied recently a subline of P388 murine leukemia cells which is resistant to Adriamycin (P388/ADR) and have compared certain properties of this subline with those of the sensitive parent line. Since Adriamycin (an anthracycline) is relatively soluble in nonpolar organic solvents, it was of interest to determine whether the difference in drug sensitivity correlated with differences in lipid composition. We noted that P388/ADR cells are also relatively resistant to other structur-
ally unrelated compounds which share solubility characteristics with Adriamycin, e.g., vincristine. Moreover, other animal cell lines have been described which also have been noted to have broad spectra of drug resistance, after having been selected for resistance to anthracycline compounds. These findings are consistent with the idea that drug resistance in these cells could be related to differences in cell composition which alter the distribution of drug within the cell.

In a preliminary study, we found that P388/ADR cells stained with Oil Red O demonstrate significantly higher quantities of intracellular lipid than do the sensitive parent P388 cells. It was thus possible that cellular resistance was, in part, caused by the ability of the cell to sequester the drug away from its macromolecular target. In addition, since Adriamycin transport into cells occurs through the lipid phase of the plasma membrane, it was possible that an alteration in cell lipid composition would also alter the properties of the membrane so as to inhibit drug entry into P388/ADR cells. Studies were therefore undertaken relating to the properties of the membrane. Electron spin resonance studies (as a function of temperature) indicated that P388/ADR cells had a higher order parameter than did the parent P388 cells, suggesting that the resistant cells had greater membrane rigidity. Fluorescence anisotropy and depolarization measurements likewise indicated more restricted motion of the probe in P388/ADR cell membranes than in those of P388 cells. Finally, whole-cell measurements indicated that larger amounts of the probe, which is lipid soluble, were taken up by P388/ADR cells than by cells of the parent line, consistent with our observations using Oil Red O staining. Direct measurements of the uptake of daunomycin (another anthracycline) into P388/ADR cells indicated that lower intracellular levels were achieved in P388, with a slower rate of uptake, consistent with the findings on membrane differences. The intracellular distribution of daunomycin in P388/ADR cells indicates that lower amounts are bound to DNA as compared to the situation in P388 cells, at the same concentration (relative to cytoxic effect). Relatively more drug is in the lipid fraction in the resistant cells. Thus, P388/ADR cells have a relatively poor transport of drug into the cell, and that drug which is intracellular tends to be sequestered away from DNA, its molecular site of action. This finding is of potential importance with respect to nutritional intervention; the P388 system suggests that it might be possible to alter dietary lipid such that the biochemical composition of drug-resistant cells could be favorably influenced. Presently, experiments are under way in which rodents are receiving a diet high in coconut oil followed by implantation of Adriamycin-resistant P388 cells to determine whether an alteration in the external milieu might favorably influence Adriamycin-resistant P388 cells.

References

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