Nutrient intake and nitrogen metabolism in cancer patients during oncological chemotherapy[1-4]

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ABSTRACT Aggressive oncological chemotherapy often impairs the nutritional status of tumor patients. To evaluate the pathogenetic mechanisms, food intake in 13 cancer patients was investigated in correlation with nitrogen losses, N balances, muscle wasting, and weight course, during cytostatic therapy. Median daily N and energy intakes were reduced only in patients with weight loss [0.55 g protein, 16.5 kcal/kg ideal body wt (IBW)]. Patients with constant weight had the same intake as control subjects (1.27 g protein, 37.2 kcal IBW). N balances and creatinine height index (CHI) correlated with daily nutrient intake. Fecal N excretions did not correlate with urinary losses; there was no excess of fecal N loss because of cytostatic treatment. The impairment of cancer patients' nutritional status seems to depend primarily on the decrease of spontaneous oral intake as a consequence of the side effects of tumor therapy. Changes in CHI, compared before and after chemotherapy, indicated muscle wasting of weight-losing patients. *Am J Clin Nutr* 1989;50:454–9.

KEY WORDS Nitrogen metabolism, nitrogen balance, nitrogen excretion, malnutrition in cancer, oncological chemotherapy, supportive tumor therapy, feeding behavior, nutritional assessment, creatinine height index, anorexia

Introduction

Weight loss is one of the clinical characteristics of progressive malignancies. The tumor burden itself may induce anorexia with reduced spontaneous oral intake as well as hypermetabolism of the tumor-bearing host (1, 2). Furthermore, aggressive antineoplastic regimens often impair the nutritional status of a tumor patient (3). Until now there was no definitive answer to the question, which of the following factors is the prime inducement of the therapy-associated malnutrition: the diminished food intake because of anorexia or other side effects of tumor treatment, or changes of N metabolism during polychemotherapy? N intake and N balance (NB) are of prime importance for metabolic processes and for the patients' nutritional status and well-being. Nevertheless, there are only few systematic investigations with special respect to the nitrogen metabolism of the tumor-bearing host during oncological chemotherapy. In particular, N wastes via feces have not been studied yet in this situation. Therefore, our aim was to investigate the influence of multitherapeutical antineoplastic regimens on food intake and N metabolism with special respect to changes in urinary and fecal output of total N and N metabolites.

Subjects and methods

Subjects

Thirteen consecutively treated tumor patients were investigated in the course of antineoplastic treatment and compared with 12 healthy volunteers. The procedures followed were in accord with the Helsinki Declaration as updated in Tokyo, Japan 1975. Clinical data of the subjects and the oncological regimens are listed in **Tables 1–3,** they include the regimens' references. Exclusion criteria were diarrhea, liver insufficiency, and impaired renal function.

All patients got the usual hospital diet and received free intake of formula diet (Biosorb® drink, Pfrimmer Co, Erlangen,

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TABLE 1
Chemotherapeutic regimens

Diagnosis	Patient	Reference	Drugs*
Acute myelogenous leukemia	1–7	4	Cytarabin, daunorubicin, and vincristine
Hodgkin lymphoma	8	5	Cyclo-phosphamide, vincristine, procarbazine, and prednisone
Teratocarcinoma	9	6	Ifosfamide, etoposide, and cis-platin
Gastric carcinoma	10–12/1	7	Methotrexate, fluorouracil, and adriamycin
Gastric carcinoma	12/2†	—	Adriamycin, fluorouracil, etoposide, and cis-platin
Oat cell carcinoma	13	8	Adriamycin, cis-platin, and vincristine

* Adriamycin: Adriblastin®, Farmitalia, Freiburg, FRG; cis-platin: Platinex®, Bristol-Myers, Troisdorf, FRG; cyclophosphamide: Endoxan®, Degussa, Bielefeld, FRG; cytarabin: Alexan®, Mack, Illertissen, FRG; daunorubicin: Daunoblastin®, Farmitalia, Freiburg, FRG; etoposide: Vepesid®, Bristol-Myers, Troisdorf, FRG; fluorouracil: Fluroblastin®, Farmitalia, Freiburg, FRG; ifosfamide: Holoxan®, Degussa, Bielefeld, FRG; methotrexate: Methotrexat®, Cyanamid, Wolfratshausen, FRG; prednisone: Decortin®, Merck, Darmstadt, FRG; procarbazine: Natulan®, Roche, Grenzach, FRG; and vincristine: Vincristin®, Bristol-Myers, Troisdorf, FRG.

† P Dias Wickramanayake, unpublished observation, 1986.

FRG; Salvimulsin®, Boehringer Mannheim, FRG; and Nutricomp®F, Braun Inc, Melsungen, FRG) as supplements. The volunteers recorded their usual food intake over 6 d. The daily food intake of the patients was evaluated by a dietician who controlled the leftovers of each meal as well as the patients' and the volunteers' daily food intake records. From that the daily intake of protein (N) and energy was calculated by using standard tables (9).

Biochemical investigations

The biochemical investigations were done in volunteers on each day of the food intake recording time (ie, 6 d); 2 d before the onset of therapy, and during the whole therapy period (median, 9 d, range, 7–16 d) in patients. The 24-h total N output via the concurrently collected urine and feces was measured by using the chemiluminescent N detection method (10) (Antek 703 C, Antek Instruments Inc, Houston, TX). Analyses of serum and 24-h urinary concentrations of urea and creatinine were performed in an automatic analyzer (model 704-737, Hitachi, Mountain View, CA). NBs were calculated from the data of 24-h food intake and 24-h N wastes. Miscellaneous N losses were estimated to be 35.7 mmol/d (11); changes in body water urea N were taken into consideration by using a correction factor (12). The creatinine height index (CHI) was calculated according to Blackburn et al (13) by using 24-h urinary creatinine excretion before and after chemotherapy. The CHI is an indicator of muscle mass during a steady state. Changes in the CHI, when compared before and after tumor treatment, could indicate muscle wasting during therapy. To obtain a steady state of creatinine excretion, meat intake was avoided during the collection periods (14).

Statistics

For statistical evaluation we used the median test because of the heterogeneity of the investigated groups. All values are

TABLE 2
Data for the tumor patients before therapy*

Patient	Sex	Age	Diagnosis	Stage and classification	Body weight	CHI
		y			*% IBW*	*% ref*†
1	F	53	AML	M1	96	109
2	F	53	AML	M2	108	109
3	F	48	AML	M2	101	113
4	M	35	AML	M2	85	83
5	M	52	AML	M1	102	83
6	M	39	AML	M2	118	105
7	M	56	AML	M3	114	81
8	M	35	HL	IVA	91	97
9	M	20	TC	pT4N3	96	102
10	M	55	GC	T4N3M0	105	86
11	M	58	GC	T4N3M0	111	96
12/1	M	56	GC	T4N2M0	108	88
12/2	M	56	GC	T4N2M0	100	65
13	M	55	OCL	T3N3M0	108	95
Median		53	—	—	105	96

* IBW, ideal body weight (12); CHI, creatinine height index (13); AML, acute myelogenous leukemia; HL, Hodgkin lymphoma; TC, testicular teratocarcinoma; GC, gastric carcinoma; and OCL, oat cell lung carcinoma.

† Percent of reference value.

TABLE 3
Data for the control subjects

Subject	Sex	Age	CHI	Body weight	Nitrogen balance*	Protein intake*	Energy intake*
		y	*% ref*†	*% IBW*	*g/24 h*	*g·kg IBW^{-1}·24 h^{-1}*	*kcal·kg IBW^{-1}·24 h^{-1}*
1	F	27	95	93	+0.1 (−1.43 to +0.84)	0.83 (0.66–1.2)	44.1 (41.7–48.4)
2	F	25	101	104	−0.73 (−1.21 to +1.47)	1.04 (0.69–1.09)	35.1 (31.6–39.9)
3	F	32	116	90	+1.18 (−1.4 to +1.9)	0.96 (0.82–1.1)	44.8 (33.1–46.7)
4	F	26	97	95	−0.3 (−1.2 to +1.64)	1.3 (1.06–1.4)	41.8 (33.2–47.5)
5	F	25	97	94	+0.63 (−1.27 to +1.8)	1.2 (1.19–1.4)	41.8 (32.3–53.2)
6	F	25	102	92	+0.9 (−1.4 to + 1.29)	1.9 (1.78–2.62)	48.5 (36.1–63.1)
7	F	25	90	110	−1.1 (−1.56 to +0.97)	1.39 (0.96–2.4)	44.3 (31.9–58.4)
8	F	24	109	104	−0.33 (−1.69 to +0.43)	0.83 (0.6–0.9)	44.8 (44.3–48.3)
9	F	25	101	100	+0.35 (+0.34 to +0.69)	1.58 (1.31–1.6)	47.2 (37.6–50.6)
10	M	24	111	103	−1.31 (−2.61 to +0.13)	1.14 (1.07–1.28)	32.1 (26.4–45.3)
11	M	31	95	105	−0.45 (−2.1 to +1.6)	1.28 (0.65–1.39)	35.1 (26.6–56.9)
12	M	25	100	91	+0.8 (−0.67 to +0.81)	1.21 (0.84–2.1)	38.6 (27.7–50.8)
Median		25	101	97	−0.1	1.2	36.9

* Medians; ranges in parentheses.
† Percent of reference value.

expressed as medians and ranges, respectively [99% confidence ranges (CRs)]; p values < 0.05% were considered significant.

Results

The results are listed in **Tables 4–6.** During oncological therapy, patients with constant or increased body weight were those with well-balanced or positive N balance. Before chemotherapy all patients and control subjects had a CHI within the normal range (13). After the end of therapy, medians and CRs were 67% of the initial values (50–87%) for the subjects with weight loss and 99% (99–105%) for those without. During cytostatic treatment the creatinine output was heterogenous: 11 patients showed an increase in urine creatinine above the initial values with levels > 17.7 mmol/d in 5 of the subjects (patients 2, 6, 9, 10, and 11).

Before the onset of therapy, the total daily intake of all patients (Table 2) was significantly below that of the control subjects (Table 3) but higher than during cytostatic treatment. Median pretherapeutic energy intake was 1941 kcal/d (99% CR, 1470–2100) for the tumor patients and 2336 kcal/d (99% CR, 2065–2715; $p < 0.001$) for control subjects; during chemotherapy energy intake was 1540 kcal/d (99% CR, 1146–1916). During chemotherapy the daily energy and N intake of the weight-los-

TABLE 4
Data for patients without weight loss during therapy, daily intake and nitrogen balances during therapy, and creatinine height index, (CHI) and body weight after therapy

Patient	Days of therapy	CHI	Weight change	N balance*	Protein intake*	Energy intake*
		% ref†	*% initial body wt*	*g/24 h*	*g·kg IBW^{-1}·24 h^{-1}*	*kcal·kg IBW^{-1}·24 h^{-1}*
1	6	99	100	−0.1 (−4.0 to +0.8)	1.27 (0.9–1.8)	37.2 (25.5–59.6)
3	10	100	100.8	+2.4 (−5.5 to +4.7)	1.44 (0.86–1.9)	37.3 (26.4–45.4)
6/2‡	8	99	100	+9.5 (+5.4 to +10.6)	1.75 (0.63–2.0)	52.1 (14.6–54.3)
7	14	99	100	+0.6 (−0.7 to +2.9)	1.47 (0.32–1.61)	40.0 (38.4–44.6)
10	6	105	101.3	+2.1 (−4.6 to +4.2)	1.18 (1.0–1.7)	30.7 (25.2–38.8)
12/2§	7	57	103.4	−16.3 (−18.0 to −0.3)	0.9 (0.68–1.17)	29.7 (22.0–31.7)
13	6	99	102	+0.1 (−3.1 to +2.2)	0.88 (0.78–1.4)	28.7 (22.0–29.0)
Median	7	99	100	+0.6	1.27	37.2

* Median; ranges in parentheses.
† Percent of reference value.
‡ Acute myelogenous leukemia, consolidation therapy.
§ Gastric cancer, infusion therapy.

TABLE 5
Data for patients with weight loss during therapy, daily intake and nitrogen balances during therapy, and creatinine height index (CHI) and body weight after therapy

Patient	Days of therapy	CHI	Weight change	N balance*	Protein intake*	Energy intake*
		% ref†	*% initial body wt*	*g/24 h*	*g·kg IBW^{-1}·24 h^{-1}*	*kcal·kg IBW^{-1}·24 h^{-1}*
2	7	87	98.4	−10.3 (−15.4 to −6.6)	0.26 (0.08–0.68)	16.1 (4.1–18.2)
4	7	60	92.9	−8.4 (−12.2 to −4.6)	0.1 (0.1–0.49)	13.0 (4.9–17.9)
5	9	61	97.2	−8.4 (−19.9 to −0.2)	0.97 (0.6–1.75)	20.8 (14.3–44.2)
6/1‡	8	54	91.7	−34.4 (−41.2 to −9.2)	0.06 (0–0.57)	2.2 (0–82)
8	6	78	98.1	−7.3 (−16.1 to +1.5)	0.76 (0.67–1.28)	22.4 (19.1–30.1)
9	11	78	98.2	−10.6 (−14.3 to −2.3)	0.51 (0–1.65)	11.8 (0–47.7)
11	6	78	98.9	−7.8 (−8.2 to +0.5)	0.72 (0.35–0.97)	19.9 (12.4–27.0)
12/1	5	65	98.9	−6.3 (−8.9 to 3.1)	0.58 (0.34–1.5)	16.9 (14.0–29.4)
Median	7	73§	98.1	−8.4§	0.55§	16.5§

* Median; ranges in parentheses.
† Percent of reference value.
‡ Acute myelogenous therapy, induction therapy.
§ $p < 0.001$, patients with weight loss vs patients with no weight loss and control subjects.

ing patients was lowered to 36.1%; 40% that of the control subject's intake. Patients without weight loss were able to eat more than twice as much as those with weight loss, ie, as much as control subjects (median intake: 1.2 g protein/kg·kg IBW^{-1}·24 h^{-1} for a total of 36.9 kcal; IBW, ideal body weight). The laboratory findings for the control group were in good accordance with those in the literature (15). The NBs of weight losing patients were far below the NBs of the control subjects and those with constant weight (median: −0.1 g N/24 h, CR −1.9 to +0.9). Although the fecal weight of patients and control subjects was not different, the median daily fecal N output of the tumor patients during chemotherapy (0.98 g/d, 99% cr 0.75–1.5) was significantly below that of the control subjects (1.52 g/d, 99% cr, 1.0–2.2; $p < 0.0001$). Regarding the side effects of the antineoplastic treatment, one patient without weight loss (patient 1) suffered from mild fever (body temperature < 38 °C) for 4 d. Mild mucositis for 2 d was mentioned by patient 3 and intensive nausea and vomiting for 3 d was reported by patient 12/2.

Four patients with weight loss (patients 2, 5, 6, and 8) had body temperatures > 38 °C for 4, 5, 4, and 7 d, respectively. Patients 11 and 12/1 had intensive oral mucositis.

Discussion

Oncological chemotherapy has a deleterious effect not only on tumor tissues but also on the metabolism of the tumor-bearing host. Regarding nutritional status, tumor therapy may affect the spontaneous oral intake via anorexia (2, 16–22) and the absorption and assimilation of the nutrients (23, 24) too. Our data do not show any uniform influence of the types of tumor illnesses and ther-

TABLE 6
Daily intake and data of nitrogen metabolites in tumor patients and healthy volunteers

Index	Control subjects*	Tumor patients*	*p*
Fecal weight (g/24 h)	140 (95–180)	125 (85–136)	NS
Fecal N (mmol/d)	108.5 (71.4–157.0)	70.0 (53.5–107.1)	<0.0001
Urine volume (mL/24 h)	1600 (1250–1900)	1750 (1400–2900)	<0.01
Urinary creatinine (mmol/d)	12.4 (7.1–15.0)	12.4 (8.0–15.9)	NS
Urinary uric acid (mmol/d)	2.8 (2.6–3.4)	3.2 (2.6–3.8)	NS
Urinary urea (mmol/d)	318.1 (269.8–363.1)	293.1 (256.5–353.1)	NS
Urinary N (mmol/d)	920.8 (792.3–1199.2)	706.7 (578.2–1020.7)	<0.001
N intake (g/24 h)	13.1 (10.6–15.0)	9.9 (3.9–14.4)	<0.01
Energy intake (kcal/24 h)	2336 (2065–2715)	1540 (1146–1916)	<0.0001
N balance (mol/d)	−0.007 (−0.14 to +0.06)	−0.37 (−0.65 to +0.23)	<0.01

* Medians; 99% confidence ranges of all subjects on all study days in parentheses.

apy on the nutritional indices. Individual factors of each patient, eg, anorexia and inability to ingest oral nutrition because of the side effects of tumor treatment, seem to be much more relevant than are metabolic influences of the investigated tumors (25). Fever was the main factor correlating with inadequate oral intake, other patients suffered from significant oral mucositis.

There is a strong correlation between the amount of food intake and the nutritional status of the tumor patients. Only those subjects who were able to eat the same amount as control subjects during chemotherapy maintained body weight, CHI, and a positive NB. Protein and energy intake of the weight-losing patients decreased to the same extent during the therapeutic period. These results suggest that caloric intake predicts for weight change status. As a consequence one may not need to know either protein intake or NB to identify the patients who might benefit from intensive nutritional intervention, eg, enteral or parenteral feeding. The negative NBs of the anorectic tumor patients are much lower than those of healthy young men with comparable reduced daily food intake (26). The effects of the cytostatic agents on the tumor-bearing host (27) seem to overcome the physiological protein-sparing mechanisms. The induction therapy of acute myelogenous leukemia (AML) (4) is the treatment with the most deleterious effect on the patients. Very high amounts of N and energy are necessary to maintain the nutritional integrity, as already shown (28).

For the first time we were able to investigate systematically the fecal N output during cytostatic treatment. Several studies postulate an impaired nutrient absorption as a consequence of oncological chemotherapy (23, 24, 29, 30). In contrast to the expected increase of fecal N loss, we found a significantly reduced fecal N output proportionate to the decrease of N intake.

There are different factors influencing the composition of the feces, the N content of which is closely correlated with the fecal weight (31): ~60% of the total fecal N originates from the microbial content of the stool (32). Mucosal desquamation and nonabsorbed food residues account for most of the remainder. During cytostatic treatment a reduced food intake as well as a sterilization of the gastrointestinal tract may be responsible for our results. We conclude that orally or enterally applied nutrients will be assimilated sufficiently in most of the patients during cytostatic therapy. The data on CHI show that the weight loss during oncological chemotherapy may be primarily a problem of muscle wasting. Other body compartments, eg, total-body water, can expand in this situation. That is why the degree of malnutrition is only reflected insufficiently by the loss of weight. CHI seems to be useful to discriminate between well nourished and malnourished subjects before and after chemotherapy (33). During the aggressive treatment the creatinine excretion increased transiently in several patients, apparently as a consequence of acute muscle wasting. That is why CHI is not a reliable indicator of the nutritional status during the application of antineoplastic therapy. In this respect our data are comparable with results obtained from patients with other types of stress metabolism (34).

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