Non-surgical oncology – Guidelines on Parenteral Nutrition, Chapter 19

Nichtchirurgische Onkologie – Leitlinie Parenterale Ernährung, Kapitel 19

Abstract

Reduced nutritional state is associated with unfavourable outcomes and a lower quality of life in patients with malignancies. Patients with active tumour disease frequently have insufficient food intake. The resting energy expenditure in cancer patients can be increased, decreased, or remain unchanged compared to predicted values. Tumours may result in varying degrees of systemic pro-inflammatory processes with secondary effects on all significant metabolic pathways. Therapeutic objectives are to stabilise nutritional state with oral/enteral nutrition and parenteral nutrition (PN) and thus to prevent or reduce progressive weight loss. The maintenance or improvement of quality of life, and the increase in the effectiveness and a reduction in the side-effects of antitumor therapy are further objectives. Indications for PN in tumour patients are essentially identical to those in patients with benign illnesses, with preference given to oral or enteral nutrition when feasible. A combined nutritional concept is preferred if oral or enteral nutrition are possible but not sufficient. There are generally no accepted standards for ideal energy and nutrient intakes in oncological patients, particularly when exclusive artificial nutrition is administered. The use of PN as a general accompaniment to radiotherapy or chemotherapy is not indicated, but PN is indicated in chronic severe radiogenic enteritis or after allogenic transplantation with pronounced mucositis or GvH-related gastrointestinal damage for prolonged periods, with particular attention to increased risk of bleeding and infection. No PN is necessary in the terminal phase.

Keywords: tumour, radiotherapy, chemotherapy, stem cell transplantation

Zusammenfassung

Ein reduzierter Ernährungszustand ist mit einer eingeschränkten Prognose und verminderter Lebensqualität assoziiert. Patienten mit aktiver Tumorerkrankung haben häufig eine unzureichende Nährstoffaufnahme. Der Ruhe-Energieumsatz kann im Vergleich zum Erwartungswert unverändert, gesteigert oder vermindert sein. Bei manifesten Tumorerkrankungen kommt es in unterschiedlichem Ausmaß zu systemischen proinflammatorischen Prozessen mit sekundären Auswirkungen auf alle wesentlichen Stoffwechselwege. Durch eine parenterale Ernährung (PE) soll der Ernährungszustand stabilisiert und ein fortschreitender Gewichtsverlust verhindert oder reduziert werden. Weitere Ziele sind der Erhalt oder eine Verbesserung der Lebensqualität und eine Erhöhung der Effektivität sowie eine Reduktion von Nebenwirkungen der antitumoralen Therapie. Prinzipiell sind die Indikationen für eine PE bei Tumorpatienten identisch mit den Indikationen bei Patienten mit gutartigen Erkrankungen, wobei bei Tumorpatienten eine orale oder enterale Nahrungszufuhr immer vor einer PE eingesetzt werden sollte. Bei möglicher oraler oder enteraler Zufuhr ergibt sich ein kombiniertes Ernährungskonzept. Für

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die optimale Energie- und Nährstoffzufuhr onkologischer Patienten, besonders für die ausschließliche künstliche Ernährung, gibt es keine allgemein akzeptierten Standards. Der generelle Einsatz einer PE begleitend zum Strahlentherapieverfahren oder zur Chemotherapie ist nicht sinnvoll, ist jedoch indiziert bei chronischer schwerer radiogener Enteritis oder nach allogener Transplantation wegen einer ausgeprägten Mukositis und GvH-bedingten Gastrointestinalschäden mit besonderer Rücksicht auf das erhöhte Blutungs- und Infektionsrisiko. In der Sterbephase ist keine PE erforderlich.

Schlüsselwörter: Tumor, Radiotherapie, Chemotherapie, Stammzelltransplantation

The nutritional state influences the clinical outcome

- Reduced nutritional state is associated with unfavourable outcomes and a lower quality of life in patients with malignancies (IIa).

Commentary

Adult tumour patients who have lost weight or are malnourished show an unfavorable outcome in longitudinal studies. The response to antitumor treatment is decreased while treatment-associated side effects are more frequent; physical performance and quality of life are compromised; overall survival is significantly shorter than in patients without weight loss [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11]. Cachexia is the most common cause of death in tumour patients other than sepsis [12]. In a recent study body nitrogen content was found to be the strongest predictor for protection against bone marrow toxicity during chemotherapy in patients with breast cancer [13].
The effect of malnutrition on the rate of cure in children with cancer is controversial. While a significantly lower rate of healing is reported in malnourished patients (Ib) [14], [15], [16], [17], [18], there appears to be no influence on patients' survival (IIa) [19], [20], [21], [22]. These differences depend on the various definitions of malnutrition, the type and extent of the tumour, tumour therapy, supportive measures and the socio-economic status of the family. Malnutrition is known to decrease immunocompetence (IIa) [23], [24], decrease the tolerance to chemotherapy (IIa) [25] and increase the rate of infection (IIa) [26], [27]. Information on organ dysfunction as a result of malnutrition in children with cancer is scarce. In malnourished children there is an increased risk of cardiomyopathy after the administration of anthracyclines (IV) [28].

Influence of malignancies on energy expenditure

- Patients with active tumours frequently have insufficient food intake (II).
- The resting energy expenditure in cancer patients can be increased, decreased, or remain unchanged in comparison to the predicted value (II).

Commentary

Food intake is lower than the usual even in patients with early stage tumour disease, and there is often a large discrepancy between the actual energy and protein intake and the calculated requirements in advanced tumour stages [10], [29].
In approximately 25% of patients with active tumours, resting energy expenditure (REE), as measured by indirect calorimetry, is more than 10% above, and in another 25% more than 10% below the predicted value. A prediction as to the direction and extent of the deviation is not possible [30], [31]. The mean value of total energy expenditure in cancer patients is similar to that of a healthy reference group [31], [32]. Studies in patients with various tumour entities showed a normal REE in people with stomach or colorectal carcinomas, and an increased REE in patients with pancreatic or bronchial carcinomas [33], [34], [35], [36]. More detailed investigations in patients with advanced bronchial and pancreatic carcinomas revealed an increased REE coupled with diminished physical activity and a slightly lower overall energy expenditure when compared to healthy subjects [35], [36].
Therefore, in adult patients normal energy expenditure should be assumed if the actual resting energy expenditure cannot be measured in individual cases. Formulae (i.e. Harris Benedict, cf. chapter "Energy expenditure and energy intake" (http://www.egms.de/en/gms/2009-7/000084.shtml)) may be used to calculate the normal resting energy expenditure. In patients, the overall energy requirement is also determined by physical activity and may be estimated as 100–120% of REE (cf. chapters "Energy expenditure and energy intake" (http://www.egms.de/en/gms/2009-7/000084.shtml) and "Neonatology/Paediatrics" (http://www.egms.de/en/gms/2009-7/000074.shtml) for children's energy expenditure).
Studies have shown that children with leukaemia have a near normal resting energy expenditure at diagnosis and during anti-cancer treatment [24], [37], [38], [39], [40]. Resting energy expenditure, however, is increased in leukaemic children with large tumour mass [38], and

in children with solid tumours [24], [41]. However, the data are inconsistent.

Malignancies may influence metabolic parameters

Clinically-relevant metabolic changes

Manifest tumours result in varying degrees of systemic pro-inflammatory processes with secondary effects on all significant metabolic pathways [42]. A large body of data suggests that the primary reaction of the tumour-bearing host is to release cytokines, catabolic hormones and other regulatory peptides locally and systemically [42], [43], [44].
The resulting systemic inflammatory reaction contributes significantly to the loss of appetite [45], [46] and weight [47], [48], [49], [50]. These cytokine-induced metabolic changes prevent a recovery of body cell mass [51], and are associated with reduced life expectancy [52] in cachectic patients [52], [53].

Effects on carbohydrate metabolism

- Insulin resistance and increased glucose production can often be detected in tumour patients (II).

Commentary

Impaired glucose tolerance due to insulin resistance is common in tumour patients [54]. The plasma ratio of insulin to catabolic hormones is abnormal with typical findings of increased cortisol secretion and a decreased insulin-cortisol ratio [44], [55]. This results in increased glucose turnover and gluconeogenesis [43]. Concomitant medication with high-dose glucocorticoids intensifies these changes.

Effects on lipid metabolism

- Weight loss in cancer patients is accompanied by a loss of lipid stores and increased serum triglycerides. The ability to oxidise lipids is normal to increased (II).

Commentary

The reasons for changes in lipid metabolism have not yet been clearly determined [44] although increased lipolysis is often observed [56], [57]. Increased [57], [58], [59] or at least normal [60], lipid oxidation is often detectable at the same time, while glucose oxidation is compromised. These observations may support the recommendation to increase the lipids to glucose ratio when composing nutrition for cancer patients.

Effects on protein metabolism

- Protein expenditure is usually increased, resulting in a loss of muscle mass and an increased production of acute phase proteins (II).

Commentary

While the underlying processes are complex, usually increases in overall body protein turnover and in proteolysis are measured [43], [61]. The ATP consuming and ubiquitin-dependent proteolysis system of proteasomes is activated at an early stage [62], [63], [64]. These changes are triggered by inflammatory mediators and, possibly, additional substances released by the tumour [65], [66].

Treatment aims for parenteral nutrition (PN) in cancer patients

- PN should stabilise the nutritional state and prevent or reduce progressive weight loss (C).
- PN should maintain or improve the quality of life (C).
- PN might increase the effectivity and reduce the side-effects of anti-cancer therapies (C).

Commentary

After curative antitumour treatment, PN can enhance survival chances in patients with severe gastrointestinal defects e.g. with radiation enteritis [67]. Due to the accompanying non-specific inflammatory processes in patients with active cancers anabolism usually cannot be achieved by only supplying energy and substrates [44], [50], [51]. According to data collected on body compartments, artificial nutrition results in a stabilisation of or an increase in body weight [68], [69], [70], [71] and body fat mass, while an improvement in lean body or muscle mass is observed only rarely [72].
Numerous studies reported a median overall survival of 50 to 150 days [69], [70], [71], [73], [74], [75], [76], [77], [78] when using PN in patients with advanced cancer and chronic small bowel defects. In the majority of these patients weight [69], [70], [71], and parameters to measure quality of life may be stabilized [69], [70], [71], [75]. The rate of PN-associated infectious complications is between 0.34 and 2.68 per 1000 catheter days [74], [76], [77], [78].
Orreval et al. reported that the provision of home PN was perceived as a positive alternative to progressive weight loss due to the inability to eat in a small group of patients with advanced tumours [79].
Meta-analyses indicate that PN may reduce postoperative complications in malnourished, but not in normally nourished, patients after extensive abdominal surgery [80]. In contrast, only few studies have evaluated the influence of PN on the therapeutic effects of non-surgical oncology. Parenteral nutrition in orally nourished patients undergoing chemotherapy may increase body weight [68]

(Ib), but does not improve anticancer treatment [68], [81] (Ib). The quality of these few studies, however, is restricted by the inhomogeneity of the patient groups and by the inclusion of patients without malnutrition or patients who were able to eat normal amounts of food [81].

Indication for parenteral nutrition in cancer patients

Indications for PN in tumour patients are essentially identical to those in patients with benign illnesses. Considering the limited data available in this area [82], [83], [84], [85], [86], [87], [88] the following recommendations are given:

- PN is indicated if oral and enteral food intake [83], [84] provide <500 kcal per day and this is expected to continue for >5 days, or for between 3 and 5 days in case of severe malnutrition, or if oral and enteral food intake reach <60% of calculated requirement and this is expected to last for 10–14 days in adult patients (C).
- PN should be commenced immediately when indicated, and increased to target dosages over 2–4 days if considered necessary (C).
- The amount of PN should supplement oral or enteral nutrition, providing full nutritional requirements in combination (C).
- PN in children is indicated (C):
  - in severe malnutrition
  - in borderline malnutrition and high risk for malnutrition through therapy, etc.
    - when oral food intake is <60% of the energy and protein requirements and there is a high risk for treatment-induced malnutrition, etc.
- PN is used in children if digestion or absorption of food is impaired and it is expected that the patient will require nutritional therapy for at least 7 days. PN should be commenced as soon as possible and continued until the gastrointestinal tract is fully functioning. Regular checks should be carried out if it is expected that the patient will require a nutrition therapy for less than 7 days (C).

Commentary

In tumour patients, who are not able to eat, digest or absorb foods, the nutritional state may be maintained or improved by PN [71], [75], [89], [90], [91]. This includes situations with severe intestinal defects caused by radiation enteritis, chronic ileus, severe adhesions, short bowel syndrome, peritoneal carcinosis or the occurrence of chylothorax.

In 1994 Klein and Koretz analysed several prospective randomised-controlled studies on the effects of PN regimes in tumour patients, including 22 studies on perioperative nutrition, 18 studies using PN during the course of chemotherapy, and 4 studies using PN during radiotherapy [81]. They found no general advantage of PN regarding morbidity or mortality, but an increased rate of infection in patients receiving chemotherapy.

Definitive conclusions on the role of PN in the three treatment modalities, however, were not possible due to major flaws in most studies. Most studies had included only few subjects of heterogeneous patient groups undergoing various antitumor therapies. Individual studies were not comparable as they had used different criteria for initiation of artificial nutrition as well as different nutrition regimens and different treatment durations. In addition, patients in these studies were treated despite having a normal, or only a slightly impaired, nutritional state [85], [86].

PN increases tumour cell proliferation [92], [93], [94], [95], [96], [97] and sensitivity to chemotherapy [94], [97] in in-vitro models. In malnourished patients with gastric cancer, concomitant administration of PN with preoperative chemotherapy improved nutritional state, reduced post-operative complications, but did not influence the pre-operative tumour cell proliferation [97].

Using PN during tumour therapy improved the nutritional state of children (Ib) [23], [98], [99], [100]. Several studies indicate that chemotherapy is better tolerated when accompanied by PN, resulting in fewer therapy delays, dose reductions and shorter myelosuppression (Ib) [15], [100], [101], [102], [103]. However, other data suggest that the use of PN does not lower the incidence of therapy-related complications (IIa) [98], [104]. In addition, there is no evidence that targeted nutritinal therapy might increase the chance of healing [105] (UICC 34). On the contrary, PN is associated with an increased rate of infection (Ia) [106], [107]. Therefore, in nutritional therapy whenver possible preference should be given to the oral or enteral route [108].

Volume and substrate quantities in parenteral nutrition of cancer patients

- **Energy** expenditure is usually comparable to that of healthy subjects; only rarely is it necessary to supply daily energy exceeding 35 kcal per kg body weight (C) (for children's intake, cf. chapter "Neonatology/Paediatrics" (http://www.egms.de/en/gms/2009-7/000074.shtml)).
- A daily **amino acid** supply of 1.2 to 1.5 g per kg body weight is usually appropriate in cancer patients (C) (for the appropriate dose for children, cf. chapter "Neonatology/Paediatrics" (http://www.egms.de/en/gms/2009-7/000074.shtml)).
- There is no agreement on an ideal ratio of **lipids** and carbohydrates; the proportion of lipids can be above 35% of the overall energy intake without disadvantages (C).
- Glucose should be the preferred parenteral carbohydrate (B).

- **Micronutrients** should be supplied in sufficient amounts; this should not be less than the iv doses recommended for healthy persons (C).
- Monitoring of PN should be carried out following the usual protocol for all PN patients (C).

Commentary

There are generally no accepted standards for the optimal energy and nutrient intake in oncological patients, particularly when artificial nutrition is administered exclusively.

The energy intake should be adapted to the potentially increased energy requirements and the level of physical activity. Total energy expenditure of cancer patients was measured to be comparable to that of healthy subjects, even though REE was incresed in cancer patients [30]. The cause of this is perhaps an adaptive decrease in physical activity in metabolically altered cancer patients [36].

The basis for dosing macro- and micronutrients currently remains the same as for healthy persons. There is no indication that an intake of protein above the normal dose (max. 1.5 g protein/kg body weight) has an anticatabolic effect in oncological patients [109].

Tumour patients show increased lipid oxidation and utilisation of exogenously administered lipids [58]. Tumour cells preferentially utilise glucose for their energy requirements while healthy tissues display high lipid oxidation [110]. Therefore, it is recommended to increase the proportion of lipids to over 35% of the total energy supply in the nutrition of oncological patients [58]. More recent studies, however, showed that post-absorptive glucose turnover of malignant tissues is high and does not increase during an intravenous glucose infusion [111]; thus, the theoretical benefit of lipid over glucose solutions may be clinically irrelevant.

Metabolic and immunological effects of various lipid solutions (LCT, MCT) have been compared mainly in surgical environments. The postulated benefit of medium-chained triglycerides (MCT) over long-chained triglycerides (LCT) could not be established in various clinical studies [112], [113]. There are no data in cancer patients undergoing radiotherapy or chemotherapy substantiating benefits of more recently developed parenteral lipid emulsions, with increased contents of n-9 or n-3 fatty acids.

Attention should be given to providing a sufficient supply of micronutrients. The recommendations for intake in other patient population should be followed (cf. chapter "Water, electrolytes, vitamins and trace elements" (http://www.egms.de/en/gms/2009-7/000080.shtml)). There are no data supporting a clinical advantage of very high doses of micronutrients.

Special substrates

- The provision of special substrates such as glutamine, arginine, taurine, branched-chain amino acids or n-3 fatty acids is not recommended due to lack of convincing data supporting their use (C).

Commentary

Glutamine has been studied as a possible oral supplement to reduce toxic side-effects of radiation or chemotherapy [114]. Parenteral glutamine has been used in haematopoietic stem cell transplantations (HSCT). Findings to date are inconsistent.

In a randomized study of patients after allogeneic HSCT Ziegler et al. showed a significantly improved nitrogen balance, reduced infection rate and shorter length of stay (LOS) for patients supplemented with glutamine (0.57 g/kg/d) compared a control group on an isonitrogenic and isocaloric diet (Ib) [115]. In a randomized follow-up study these data, however, could only be repeated with respect to a reduction in LOS (Ib) [116]. In a later study, the same working group was not able to document any advantage of parenteral glutamine (0.57 g/kg/d) in a similar clinical situation [117] (Ib).

In a further randomised study patients after HSCT receiving 3–4 weeks of glutamine-enriched PN showed significant increases in total lymphocyte counts, T-lymphocytes, CD4 and CD8 cells, while the clinical outcome was unchanged [118] (Ib). In a randomised study in patients after autologous HSCT, high daily doses of intravenous alanyl-glutamine dipeptide (30 g glutamine) resulted in increased relapse and mortality rates as well as increased costs [119] (Ib).

One randomised study, which highlighted the possible protective role of glutamine infusions on hepatic functions during HSCT justifies further studies, especially with a focus on the prevention of veno-occlusive disease [120] (Ib).

In hematological patients undergoing intensive chemotherapy supplementation with glutamine dipeptide had no effect on hematological parameters or clinical toxicity; the glutamine group, however, showed significantly more weight gain during the study period [121].

In a randomised study of patients with acute myeloid leukaemia requiring PN supplementation with glutamine (20 g) resulted in a more rapid recovery of neutrophils after myelosuppressive chemotherapy, but no reduction in the incidence of neutropenic fever and no improvement in other immunological parameters [122] (Ib).

According to the current ASPEN guidelines [123], there is no indication for the administration of pharmacological doses of glutamine in patients after HSCT. Other recent recommendations agree with this [124].

There is only scarce evidence concerning other special substrates; particularly, there are no relevant data on the parenteral use of n-3 fatty acids.

Indications for parenteral nutrition during radiotherapy

- PN should not be used as a general accompaniment of radiotherapy (B), but PN is indicated if sufficient enteral intake cannot be achieved (B).
- PN is indicated in chronic severe radiation enteritis (C).

Commentary

During the last 10 years no prospective randomised studies have been published on the use of PN as an accompaniment to radiotherapy. So far it has not been demonstrated that routine PN during radiotherapy or radio-chemotherapy improves prognosis [81], [125], [126]. During radiation treatment, especially when treating head and neck areas, whenever possible, sufficient enteral nutrition should be supplied including the use of sip feeds or enteral tube feeding [109], [125], [127], [128].
PN is indicated if sufficient enteral nutrition is not possible, e.g. as a result of acute radioation enteritis; if nutritional deficits exist and radiation is intended to cover the upper gastrointestinal tract such that an intended PEG would need to be placed within the radiation field; and during neoadjuvant treatment, if insertion of a PEG system is not recommended, e.g. in oesophageal resections and planned gastric interposition. Chronic radiation enteritis develops in approx. 5% of cases subjected to abdominal radiation; this may be accompanied by intestinal failure, fistulae, perforation or chylous ascites and these cases frequently require long-term PN [67], [129], [130], [131], [132].
No benefit of special parenteral substrates such as glutamine has been established for radiotherapy procedures.

Indications for parenteral nutrition during chemotherapy

- The indications for PN during chemotherapy are not different from general indications in malignant diseases. Routine PN therapy as an accompaniment to chemotherapy is not indicated (B).

Commentary

In 1990 McGeer et al. published a meta-analysis on the use of PN during chemotherapy (Ia) [133]. They reported that PN is associated with a trend towards shorter survival and reduced tumour response. They concluded that routine PN is not advisable in patients undergoing chemotherapy. Klein and Koretz analysed 18 randomised studies with clinically relevant end points on the effect of PN in patients treated with chemotherapy. They concluded that there were no evident advantages of PN with regards to overall survival, tumour responses and toxicity of chemotherapy, but there was an increased rate of infection in those receiving PN (Ib) [81].
It is difficult to draw reliable conclusions from the existing data due to serious flaws in most study designs, such as insufficient number of patients treated, inclusion of extremely inhomogeneous patient groups, large variability of the nutrient solutions used, large variability of antitumor therapies, and inclusion of patients who were not suffering from malnutrition as well as patients who maintained normal oral food intake [81]. Randomised studies, i.e. by De Cicco et al, which differentiated between normal and malnourished patients undergoing chemotherapy, were able to detect an improvement in the nitrogen balance in severely malnourished patients while no effect was seen in patients without malnutrition [134] (Ib).
Recent recommendations by the American Gastroenterological Association (AGA) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have come to similar conclusions. The AGA report reviewed 19 randomised studies and concluded that PN had no influence on the survival of patients who were treated with chemotherapy or radiation treatment, although a positive influence may be possible after bone marrow transplants. Accompanying PN has an unfavourable effect on other parameters in patients treated for chemotherapy, radiotherapy or bone marrow transplants, mainly an increase in infectious complications and a decrease of the response to chemotherapy (Ib) [85].
The ASPEN recommendations specify that PN as routine accompaniment of chemotherapy is not justified and potentially dangerous due to the increased risk of infection. It is pointed out, however, that PN should be offered to patients who are malnourished and who are unable to absorb sufficient nutrients over a long time period [135].
Regarding all published recommendations it is important to note that all randomised studies on which they are based were performed more than 10 years ago and that many are flawed as mentioned above. More recent studies report fewer complications of long-term PN [67], [76], [77], [78], [136], [137], suggesting that the benefits and risks of PN administration during chemotherapy should be reviewed again in the near future.

Indications for parenteral nutrition during autologous/allogeneic stem cell transplantion

- PN is required only in selected patients after autologous transplantations, while after allogeneic transplantation PN is usually required in most patients and for prolonged time periods due to the development of pronounced mucositis and GvH-related gastrointestinal damage (C).
- Particular attention must be paid to the increased risk of bleeding and infection associated with PN (C).

Commentary

In patients after autologous transplantations impaired food intake is usually of short duration (2–3 weeks). Nutritional problems in allogenic transplant patients usually are more severe and prolonged. Thus, there is no need for routine PN after autologous transplantations, but PN may be necessary if complications develop such as prolonged mucositis [138]. After allogenic transplantations, PN is routinely administered in most transplantation centres [138]. In 1987 Weisdorf et al. showed that prophylactic standardised PN significantly improved survival three years after HSCT [106]. The control group received only minerals and vitamins intravenously until a reduced nutritional state was detected. Because patients receiving early PN had a lower relapse rate, it was speculated that the better overall survival observed might have been caused by a possible positive effect of PN on transplant function, resulting e.g. in an increased graft versus leukaemia effect.
Enteral nutrition is not well tolerated in most cases after complete conditioning regimens [139]; if tolerated, however, enteral nutrition in patients with a functioning gastrointestinal tract has effects on nutritional status that are comparable to those of PN [124], [140] [141] (Ib). The French Federation of Cancer Centres, as well as the authors of a review of relevant randomised studies recommend enteral nutrition as the primary approach in non-myeloablative conditioning, and PN only in cases of gastrointestinal complications [141]. It has been recommended to initiate PN when oral or enteral food intake provides less than 50–60% of calculated requirements [67], [141].
American and French panels on gastroenterology and nutrition emphasize that all HSCT patients carry a high nutritional risk and should, therefore, be monitored regularly for nutritional deficits before and after transplantation [123], [141].
A small randomised study has observed that a high dose of lipid (lipid:glucose ratio 80:20) after allogenic transplantation lowered the incidence of lethal acute graft–versus-host disease and hyperglycaemia [142]. This study has yet to be confirmed.
Certin et al. [143] reported that supplying total rather than partial PN after autologous transplantation resulted in a delyed rise in thrombocytes. At the same time, there were more cases of infection and hyperglycaemia associated with total PN as compared to partial PN, whilst a drop in the level of albumin was prevented. The study was not randomized and patients receiving total PN may have been more severely ill. The observation, however, may support the recommendation not to provide total PN as a standard treatment after autologous transplantations.
In children an autologous blood stem cell transplantation usually has only a low impact on nutritional status (III) [144], [145]. Thus, a targeted nutritional therapy should be based primarily on the above-mentioned criteria (see: Indication for PN in cancer patients) or be initiated if a conditioning therapy is chosen, which is associated with a high risk for severe mucositis.
In allogenic transplantations the criteria for using PN are usually given, and PN has been shown to have positive effects on maintaining the body weight [146], [147] (Ib). Enteral nutrition is possible in many cases and then is as effective as PN. In a study by Hopman et al., enteral tube feeding was possible during 60% of the study period, although it could be used as the sole form of nutrition only in 3 of 12 children [148] (Ib). In a retrospective analysis, Langdana et al. reported on their positive experiences and the high patient acceptance rate for a similar concept with the preferrential use of enteral nutrition [149] (III). In all cases the risks of enteral tube feeding (aspiration, bleeding, diarrhoea, sinusitis, intestinal perforation) should be weighed against the risks of PN (catheter sepsis and metabolic complications).
In most cases it appears to be sufficient to restrict the amount of energy provided to be slightly more than the resting energy expenditure (see: Influence of malignancies on energy expenditure) [150], [151], [152].
There are no generally accepted indications for the use of glutamine (see Special substrates).

Indications for parenteral nutrition independent of antitumor therapies in incurable cancer patients

- If food intake is insufficient survival of patients in advanced cancer stages may be compromised more by inadequate nutrition than by the underlying illness (C).
- Long-term PN should be initiated if intestinal absorption is severely impaired and if allof the following 4 criteria are fulfilled (C):

1. enteral nutrition is insufficient to maintain nutritional state,
2. the expected survival is more than 4 weeks,
3. PN is expected to stabilise or improve quality of life,
4. the patient explicitely wishes to receive PN.

Commentary

Oncological treatments today may allow patients with incurable cancer disease to survive up to a point at which further survival is significantly affected the nutritional state [153]. An inadequate oral or enteral intake results in progressive weight loss and impaired clinical outcome (see: The nutritional state influences the clinical outcome). Randomised studies on the value of PN appear unethical in these situations [87].
Despite a lack of effective antitumor treatment options, patients with advanced cancers may have a life expectancy of several weeks or months. If the expected survival exceeds 2 to 3 months (e.g. the period of survival in total starvation [154], [155], [156]), it can be reasonably assumed that PN will lengthen the survival of a patient who does not tolerate enteral nutrition [87]. In this situation

PN, by providing essential nutrition, constitutes a basic care rather than a medical therapy [87], [157].
Specialised centres providing long-term PN to patients with advanced cancer disease report a median survival period of 2–5 months [69], [70], [71], [73], [74], [75], [76], [77], [78]. This means that a large proportion of patients cared for in this manner have a longer period of survival than that assumed for conditions of complete starvation. Weight stabilisation was successful in a majority of patients [69], [70], [71].
Quality of life scores are poorer in parenterally nourished cancer patients than in healthy subjects undergoing PN; cancer patients are further burdened by accompanying depressions and opoid requirements [158]. PN, however, may stabilise parameters determining quality of life [69], [70], [71]. Orreval et al. reported that the provision of PN was perceived as a positive alternative to progressive weight loss by a small group of patients with advanced tumours and their relatives [79].
Since the benefits of PN can only have an impact when life expectancy is impaired more by insufficient food intake than by the tumour itself, several expert groups recommend considering PN when the expected survival is at least 4 weeks [135] or 2–3 months depending on the tumour [85], [87], [159], [160]. No advantage of PN should be expected when survival is shorter.
It is extremely difficult to estimate the life expectancy of a cancer patient and, hence, the possible advantages of artificial nutrition. These patients should, therefore, be seen and evaluated cooperatively by their consultant oncologist, the nutrition specialist and the palliative care consultant in order to design a treatment plan that is in agreement with the patients expectations and wishes.

Parenteral nutrition in terminally ill patients

- No PN is necessary in dying patients (B).
- The occurrence of agitated confusion induced by dehydration can be controlled by parenteral infusion of saline solutions (or the appropriate paediatric solutions, respectively) (B).

Commentary

During the phase of dying the most important aims of treatment and care are the alleviation of agonising discomfort and the feelings of thirst and hunger. Fluids and nutrition are part of the basic care; however, the patient needs to consent to such offers [157]. Most patients do not feel hungry in the terminal phase of life and only require minimal quantities of fluid [161]. It is counterproductive since it may strain the patient severely and thus it should be avoided at all cost to continue standardised infusion regimens into the terminal phase without further consideration [162].
Regulation of fluid balance should be observed closely. Both dehydration, induced by diuretics or limited drinking, and hyperhydration caused by infusions can have adverse affects on a person's well-being. The "dry mouth" is one of the main symptoms of the dying [163]. However, thirst and "dry mouth" do neither correlate with the degree of hydration [164] nor with the volume of intravenous infusion [165]. Terminal patients appear to receive too much fluid in general [162], increasing the risks for peripheral oedema, ascites, pleural effusions and the development of a pulmonary oedema.
Dehydration can result in drying of the mucous membranes with subsequent injuries and infections [163], it reduces alertness and promotes the occurrence of restlessness and confusion [166], thus contributing to the burden of the patients and their relatives [167]. Retrospective studies provided evidence that intravenous flids may reduce neuropsychiatric symptoms like sedation, hallucinations, myoclonus and agitation [168], [169]. A randomised trial in dehydrated terminal cancer patients could show that subjective discomfort was significantly improved with the infusion of 1000 ml per day as compared to no infusions and only minimal oral fluid intake of 100 ml per day [170].
Recommendations for terminal care, therefore, emphasize that fluid intake should always be prescribed on an individual basis and should target the prevention of intolerable symptoms. Fluid quantities of 1000 ml per day are recommended in symptomatic dehydration [170], [171]; in children this corresponds to supplying approx. 50% of the daily fluid requirements.

Notes

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