Nutrition 67–68 (2019) 110541

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Combining optimal nutrition and exercise in a multimodal approach for patients with active cancer and risk for losing weight: Rationale and practical approach

Tora Skeidsvoll Solheim Ph.D. [a,b,*], Ola Magne Vagnildhaug M.D. [a,b], Barry J. Laird M.D. [c,d], Trude Rakel Balstad Ph.D. [a,b]

[a] Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway
[b] Cancer Clinic, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
[c] Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK
[d] St Columba's Hospice, Boswall Road, Edinburgh, UK

ARTICLE INFO

Article History:
Received 4 April 2019
Accepted 20 June 2019

Keywords:
Cancer cachexia
Weight loss
Dietary counseling
Oral nutritional supplement
Resistance exercise
Aerobic exercise
Pharmaconutrients
ω-3 polyunsaturated fatty acids

ABSTRACT

Weight loss and functional decline is a common and detrimental consequence of cancer. The interventions that are offered to patients with weight loss and functional decline often seem haphazard and varying from center to center. The lack of stringent management is probably based both on lack of knowledge of existing treatment guidelines and the current weak level of evidence of clinical effects of different nutritional and exercise interventions. Some studies evaluated multimodal interventions with various treatment combinations, including nutrition and exercise, that report clinically significant effects on cachexia outcomes. As of today, however, there is a paucity of large randomized controlled trials that incorporate both a fully structured exercise program and a well-described nutritional intervention. Studies investigating combinations of several interventions in patients with active cancer and risk for losing weight are too few and too heterogeneous to enable firm conclusions about effect, optimal dose, or timing of interventions. However, data presented in this review suggest an overall benefit, especially if interventions are started before weight loss and loss of function become too severe. Thus, the aim of this review was to examine the evidence for combined treatments targeting weight loss in cancer patients.

Introduction

Up to 50% of patients with cancer experience loss of weight with a resulting dramatic decline in physical function [1,2]. The reasons behind this loss are complex; for some the main cause is reduced food intake or malabsorption, for others it is inactivity causing muscle atrophy, whereas for others again cancer cachexia is the main cause [3]. Commonly, several factors contribute to what the patient experiences as a wasting condition. Cancer cachexia has been defined as loss of muscle mass (and fat mass) that cannot be fully reversed by nutritional support [3]. However, this definition does not imply that optimal nutrition is unimportant in patients with cancer cachexia. The intention of the definition is merely to differentiate cachexia from starvation-related malnutrition and to acknowledge its complex pathophysiology and the variety of contributing factors that worsen patients' weight/muscle mass, appetite, food intake and physical function. The logical consequence of the complexity behind weight loss in patients with cancer is to take a multimodal approach to cachexia treatment, of which sufficient nutrition as well as physical exercise should form the basis to maintain muscle mass, strength, and function [4] (Fig. 1).

The relatively few cancer cachexia trials investigating combination treatments have generally explored the combinations of various drugs [5,6], or drugs in combination with nutrients in pharmacologic doses (pharmaconutrients) [7,8]. Few larger studies investigate more complex interventions where drugs or pharmaconutrients are combined with nutritional intervention and exercise programs [9–12]. The purpose of this review was to give an overview of clinical findings from multimodal interventions targeting weight loss in patients with active cancer and suggestions for practical approach to exercise and nutritional interventions.

* Corresponding author: Tel.: +47 728 26136, Fax: +47 72825736.
E-mail address: Tora.l.skeidsvoll@ntnu.no (T.S. Solheim).

https://doi.org/10.1016/j.nut.2019.06.022
0899-9007/

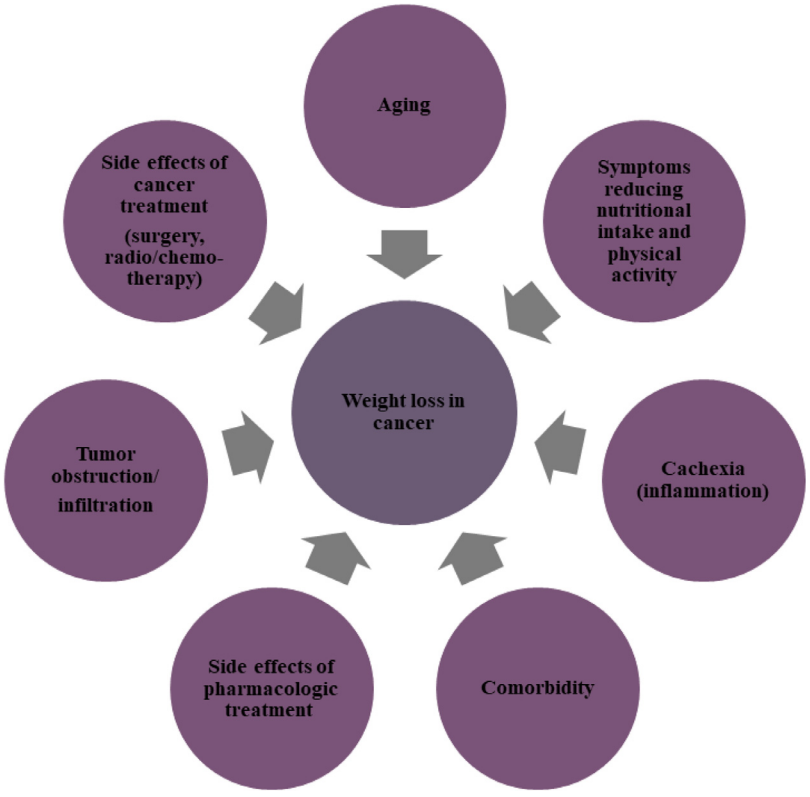

Fig. 1. Factors that can contribute to weight loss in patients with cancer.

Nutrition and pharmaconutrients

Disease-related malnutrition can be complex as it can arise from inadequate intake, increased demands, and increased nutrient loss or malabsorption, together or as isolated factors [13,14]. Nutritional support has been advocated to be the cornerstone in any cachexia treatment [3,15–17], but attempts to increase food intake alone will result in variable weight responses if hypermetabolism is apparent [18,19]. Whether individual patients are likely to respond to nutritional treatment depends on additional factors such as compliance, symptom burden, response to antineoplastic treatment, and proximity to death [18,20,21]. Inconsistent effects on body weight, energy intake, quality of life (QoL), and physical function has consequently been reported [22–24]. Positive effects on body weight have, in a recent meta-analysis, been attributed to a subset of patients given energy-dense, high-protein oral nutritional supplements (ONS) enriched with ω-3 polyunsaturated fatty acids (PUFAs) [20]. To date, ω-3 PUFAs are the most promising and well-studied pharmaconutrients in cancer cachexia and often are incorporated in ONS [15,20]. Although results have been inconclusive, and the level of evidence is weak, guidelines on nutrition in cancer support the use of fatty acids as a supplement to improve appetite and body weight [15]. Other pharmaconutrients have been investigated in cachexia, however, insufficient data exist for recommending medical use of branched-chain or other amino acids, amino acid metabolites, or L-carnitine [15]. Pharmaconutrients should never be a substitute for conventional nutritional support, and patients' basic needs should be adequately met.

Despite the various and limited effects reported, as well as uncertainties on the optimal timing and duration of nutritional intervention (in any form), meta-analysis of randomized controlled trials (RCTs) report benefits of pharmaconutrients in ω-3 PUFAs supporting energy and protein intake on body weight during chemoradiotherapy [20].

Resistance and aerobic exercise

The effect of physical exercise on patients with cancer has been the subject of many clinical studies and systematic reviews [12,25–29], and physical exercise is also shown to be safe, feasible, and effective in patients with advanced cancer [30,31]. Although studies often are small and the risk for bias high [26], there seems to be an overall positive and clinically relevant effect of exercise on several outcomes, especially on aerobic capacity, muscle strength, cancer-related fatigue, and QoL [25]. However, effect on fatigue is not more than moderate [32], and effect on QoL seems to be small [33].

Weight loss and loss of function is most common in patients with advanced cancer, but few studies have evaluated the effect of exercise on patients in this patient group [34]. An RCT testing resistance and cardiovascular training in 269 patients with mixed cancer types, of whom >50% had advanced cancer, found a small to moderate improvement of fatigue, a 10.7% improvement in VO_{2max}, and a 29.6% improvement in muscular strength [35]. Adherence to the intervention was 70.8%. In an RCT with 231 patients with incurable cancer, improvements in handgrip strength and shuttle walk test were observed after 8 wk of supervised circuit resistance and twice weekly balance and endurance training, although no effects on fatigue were observed [31]. An 8-wk resistance, endurance, and balance training (twice a week for 60 min) RCT with 30 patients with colorectal cancer undergoing palliative chemotherapy, found stabilization of neuropathic symptoms, improved strength and balance function in favor of the intervention arm [36]. A recent 6-mo, supervised resistance training study including 65 patients with pancreatic cancer reported strength

improvements in some muscle groups compared with either home-based resistance training or usual care [30].

A growing number of RCTs now show positive effects of resistance training on muscle strength and body composition in patients with advanced cancer, although most studies were conducted in breast cancer and cancer survivors [12,37,38]. Presently, it is difficult to conclude what would be the optimal exercise strategy in terms of frequency, intensity, and duration.

Pharmacologic agents and pharmaconutrients

Megestrol acetate (MA) is the pharmacologic agent that demonstrates the most consistent effects on anorexia and is one of the drugs most commonly used in trials investigating combinations of pharmacologic interventions.

In a double-blinded, three-armed study, 421 patients losing weight were randomized to one of three groups: ω-3 PUFA-enriched ONS + placebo; ONS without ω-3 PUFAs + MA; or ω-3 PUFA-enriched ONS in combination with MA. This study did not conclude that combination treatment was superior in improving weight or appetite than MA alone [39]. Equally, another study by the same research group did not find an improved effect when dronabinol was combined with MA and compared with MA alone. [40]. Conversely, a combination of MA with nonsteroidal anti-inflammatory drugs (NSAIDs) was superior in improving body weight and appetite than either of the two drugs given separately in another study [6]. Likewise, a phase III study demonstrated improved effect of a combination treatment when randomizing between five different arms: MA; ω-3 PUFA-enriched ONS; L-carnitine; thalidomide; or a combination of all the agents [41]. After a 4-mo intervention, the combination arm showed a better effect on both muscle mass and secondary endpoints (appetite, systemic inflammation, and Eastern Cooperative Oncology Group [ECOG] performance status). Another phase III study including 104 patients found that the combination treatment of MA, L-carnitine, celecoxib, and antioxidants (α-lipoic acid and carbocysteine) was superior to MA alone and improved muscle mass, resting energy expenditure (REE), fatigue, and QoL at endpoint after 4 mo [8]. However, a later phase III study, did not find added benefit on muscle mass or physical function when adding MA to an intervention including L-carnitine and celecoxib [42]. In the two previously mentioned studies, all patients received polyphenols; α-lipoic acid; carbocysteine; and vitamins A, C, and E [42,43].

A multimodal pilot study with 22 patients with advanced cancer aiming to determine maximum tolerable dose of fish oil, combined fish oil capsules (total of 6 g) with celecoxib or fish oil plus placebo [7]. All included patients received oral food supplementation. Both groups had improved appetite, fatigue, and C-reactive protein (CRP) levels 6 wk from baseline, but the combination treatment provided greater effects on CRP, muscle strength, and body weight [7]. Another combination regimen randomized 108 patients with cancer who were losing weight and reported increased body weight, REE, and exercise capacity (maximal power on a treadmill) when patients were treated with erythropoietin (EPO) in addition to indomethacin [44].

When examining studies investigating combinations of pharmacologic intervention, it is obvious that the data is very heterogeneous considering design, interventions, and results, and only rarely have high-quality RCTs been performed that validate the conclusions from studies with promising results. Therefore, it is not possible to draw conclusions about optimal combinations of pharmacologic interventions to improve body weight and physical performance.

Combination of nutrition and exercise

A few studies combining exercise and nutrition have been conducted. One feasibility study randomized 41 patients with head and neck cancer undergoing chemoradiotherapy to either standard oncologic treatment or a program consisting of 12 supervised sessions of 30 min of resistance training in combination with a minimum of one milk-based nutritional drink daily [45]. Both arms lost both weight and muscle mass, but statistically significant loss on within-group level was reported only in the control arm [45]. It is worth mentioning that 50% of the patients received nasogastric tube feeding in both groups during radiotherapy, which might influence the lack of significant effect on muscle mass in favor of the treatment arm [45]. Another feasibility study included 30 patients with head and neck cancer and prescribed identical progressive resistance exercises (30 sessions over 12 wk) to both arms. Patients in the experimental arm received 5 g carnitine and 30 g protein before each training session in addition to 7 d of pretraining supplementation [46]. There were no statistically significant differences between the arms on any outcomes. Patients in both arms increased in body weight, muscle mass, muscle strength, sit-to-stand and stair climb performance testing, and compliance were high in both arms (>90%) [46].

In palliative cancer populations, one study included 58 patients with advanced gastrointestinal or lung cancer and randomized patients to either individual nutritional counseling (e.g., use of enrichments of foods, energy, and protein-rich snacks or ONS) plus supervised resistance exercise twice a week or usual care. There were no differences in QoL, body weight, or performance testing between the arms [47]. Patients in both arms increased in body weight and improved on all performance tests with a greater improvement in the intervention arm without reaching the level of statistical significance. Energy and protein intake was assessed by 3-d food diaries and at 12 wk there was an increase in the intervention arm and a decrease in the control arm. A statistically significant difference was observed only for protein intake in favor of the intervention arm, but the clinical relevance of this difference (~8 g) is questionable as the intake at baseline was already quite high (81 g) in the entire population [47]. This study was closed prematurely due to slow accrual. A high number (63%) of eligible patients refused to participate, but patients included were considered to have good adherence to the program [47]. A single-arm feasibility and safety study in 30 older cancer patients consisted of an 8-wk low-intensity resistance training program, counseling to promote increased physical activity, dietary counseling, and a daily nutritional supplement (139 kcal·125 g·2500 mg branched-chain amino acids/L-carnitine 50 mg) [48]. A maintenance of muscle mass, calorie intake, and physical function were observed [48].

Studies investigating combinations of nutrition and exercise are very small, and several aimed at investigating feasibility and not effect on clinical outcomes. This might be the reason for the lack of reaching statistically significant results, although several studies showed a trend toward improved effect when the interventions were combined. The studies also demonstrated the importance of control groups in clinical trials, as some studies showed improvement in both arms, indicating that factors other than the studied intervention can have an effect on weight and physical function. Compliance with nutrition and exercise interventions was acceptable in all studies, with few dropouts.

Combination of nutrition and pharmacologic agents

Two RCTs by the same research group explored the effects of interventions combining individual nutrition support with

pharmacologic agents given on a patient-by-patient basis [49,50]. In one study with 309 patients with progressive cachexia, all patients in both arms were given 50 mg indomethacin daily and EPO only when hemoglobin levels were low. The intervention arm received an addition individual nutrition support when needed by counseling, ONS when food intake decreased to <90% of needs or, parenteral nutrition (PN) if intake decreased to 70% to 80% of expected needs [49]. Patients were followed until death and about 50% in the intervention arm received PN. Intention-to-treat analysis revealed statistically significant differences only in food intake and energy balance over time in favor of the nutritionally supported arm. No effects on body weight, muscle mass, fat mas, performance tests, or survival were observed [49]. Twenty-six patients in the control group received nutritional support during follow-up and were thus excluded from the per-protocol analysis, which demonstrated improved survival, fat mass, and maximum exercise capacity, but no effects on lean body mass [49]. A later RCT with 138 patients with advanced gastrointestinal malignancy demonstrated that adding insulin to a standard treatment of indomethacin (if they had increased inflammation markers), EPO (if hemoglobin was low), and nutritional support (counseling, ONS or PN) [49], significantly stimulated carbohydrate intake, increased body fat, and improved survival (median 181 versus 128 d), but did not result in a difference over time in physical activity, energy and protein intake, body weight, QoL, or fat-free mass [50].

Two RCTs investigating slightly different interventions targeting cachexia with the main use of as-needed nutrition and pharmacologic interventions (targeting inflammation, low hemoglobin, and glucose metabolism) were undertaken by the same research group. In one study, nutrition was added and in the other insulin. The studies demonstrated no effect on weight and physical activity, but both showed increased survival and fat mass (by as-treated analysis in one study) in favor of the intervention arm. Unfortunately, these results have not been confirmed by other studies, and some of the drugs (indomethacin) are no longer available.

Combination of nutrition, exercise, and pharmacologic agents

To our knowledge, only one RCT has been published in which a combination of nutrition (including pharmaconutrients), exercise, and a pharmacologic agent was tested. This was a phase II feasibility study testing a 6-wk multimodal intervention combining celecoxib, nutritional advice, two cans of ω-3 PUFA-enriched ONS daily, aerobic exercise 30 min twice per week, and resistance exercise targeting major muscle groups three times per week [51]. Forty-six patients with lung and pancreatic cancer commencing chemotherapy were randomized to either multimodal treatment or standard care. Compliance to the individual components of the intervention was 76% for celecoxib, 60% for exercise, and 48% for ONS. The multimodal intervention resulted in a stabilization of body weight, whereas patients who received standard care lost weight [51]. A phase III study following this trial is ongoing [52].

One non-randomized study included 15 patients with lung cancer and explored the effect of combining medroxyprogesterone, celecoxib, ONS, initiation and/or maintenance of a regular exercise program (type not specified), and provision of psychological/psychiatric assistance [53]. No cancer treatment was given for 4 wk before or during the 6-wk intervention. Of 15 patients, 13 were weight stable or gained weight, and improvements in caloric intake, nausea, fatigue, performance status, and appetite were reported [53]. However, only 20% of the patients followed the advice of daily exercise in this very small, single-arm study [53].

Presently, more evidence for optimal multimodal treatment including nutrition, exercise, and pharmacologic interventions is needed. However, such complicated study interventions are feasible, even in patients with advanced cancer.

Experiences from programs combining nutrition, exercise, and pharmacologic interventions

Grounded in the reasonable clinical rationale, several centers have established multimodal nutrition and exercise cachexia treatment programs as part of standard cancer care [54–57], despite a lack of major RCTs demonstrating reliable clinical effects. Some effects on improvement of symptoms such as appetite and body weight have been observed [57], and patients improving in weight or physical function also have been described more likely to improve in QoL [55,56]. Unfortunately, the nutrition and exercise interventions given in these programs often are not thoroughly described, and the attrition rate at follow-up visits introduces bias and concern considering which patients choose to come back to clinical appointments/evaluations. This is exemplified by a prospective study that evaluated a 10- to 12-wk interdisciplinary outpatient program for patients with advanced cancer. This program aimed to teach and empower patients in physical self-care and symptom management with the assistance of various specialists (physician, nurse specialist, clinical dietitian, physical therapist, occupational therapist, and if needed, a psychologist and a social worker) [54]. Of 181 included patients, 131 completed the program. Only one-fourth of the patients included had poor nutritional status at inclusion and poor nutritional status and/or CRP >20 mg/L increased the risk for not completing the program. For patients completing, 77% maintained or increased body weight and physical performance and reported improved changes in smell and taste [54].

Taken together, programs including multimodal treatments show a potential benefit that needs to be evaluated in RCTs. Challenges of adherence to a complex intervention if the patients had more advanced cachexia, emphasize the importance of early intervention.

Practical approach when combining exercise and nutrition in patients at risk for losing weight

Fundamental to any approach in patients with cancer is to have a thorough understanding of the patient's cancer disease, the patient's expected survival, and duration and consequences of tumor-directed treatment. Furthermore, it is imperative that all patients receive optimal symptom assessment and treatment, so that symptoms such as pain, nausea, or depression do not influence the patient's physical activity or nutritional intake. To improve or stabilize nutritional status and physical function, it is important to detect the decline before the losses have become too severe, as it probably is more feasible to counteract decline early in the disease trajectory [3,15]. For patients with longer expected survival, as well as for patients where cure is expected, both nutritional and exercise interventions are expected to have greater effect on QoL and physical function, and more comprehensive interventions should be prescribed.

ESPEN guidelines strongly recommend screening all cancer patients for risk for malnutrition. This also applies to patients with advanced cancer [15]. Validated nutritional screening tools identify domains of starvation-related malnutrition (weight loss, body mass index, and dietary intake), but have shortcomings regarding important cachexia domains such as muscle mass, quantification of weight loss, inflammation, fatigue, and anorexia [14,57]. Further nutritional assessment is important to quantify nutritional intake and identify nutrition-related problems. Nutritional interventions should include advice to increase oral intake if patients are able to eat, a diet enriched with energy and protein is recommended to

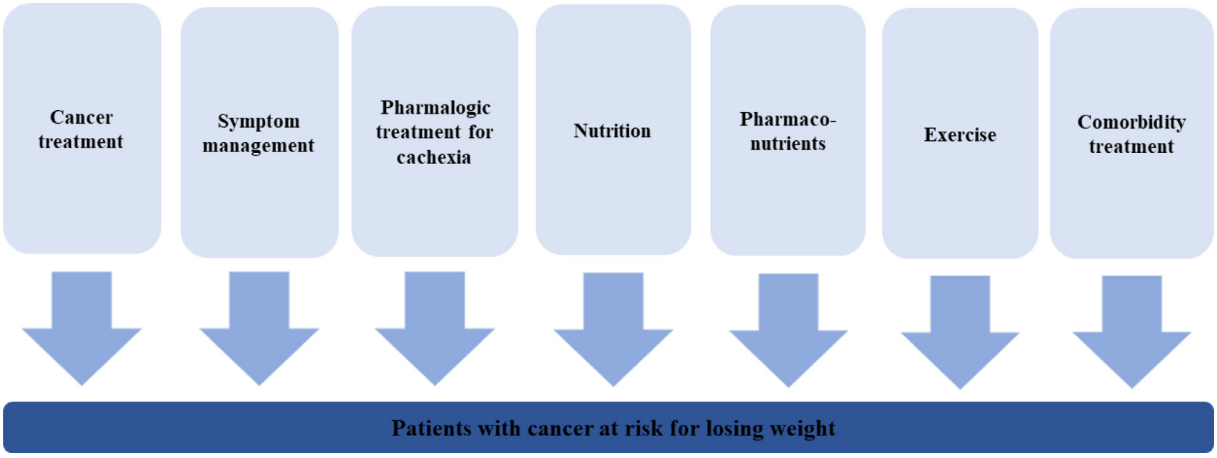

Fig. 2. Multimodal interventions in patients with cancer at risk for losing weight.

maintain or improve nutritional status [15]. Additional use of ONS, enriched with ω-3 PUFAs if available, is advised when diet alone is not sufficient to reach nutritional goals [15]. Tube feeding or PN is indicated when intake is <60% of requirements for >1 to 2 wk or if enteral feeding is not feasible (e.g., compromised gastrointestinal function) [15]. Artificial nutrition in patients with advanced cancer and loss of appetite should be carefully considered with regard to prognosis and expected benefit on QoL and potential survival.

Guidelines recommend resistance exercise in addition to aerobic exercise to maintain muscle mass and strength [15]. Considering the beneficial effects of physical activity, it is equally important to monitor physical activity as nutritional status. Physical activity is well tolerated and safe at different stages of cancer. Patients with cancer should avoid a sedentary lifestyle and should be instructed to follow the guidelines for the general population, which include supervised or home-based moderate-intensity aerobic training three times per week in addition to resistance exercise [15].

In addition to ensuring adequate energy and protein intake and physical activity, multimodal treatment should ideally include pharmacologic and pharmaconutritional treatment targeted at reversing the pathophysiologic mechanisms of cachexia development (Fig. 2). However, to our knowledge, there are no specific pharmacologic interventions that can be recommended. Corticosteroids and MA are the drugs that most consistently have shown effect on appetite, but they convey a risk for side effects and have no or only little effect on weight and physical function [58,59].

If the patient has short expected survival and has entered a refractory cachexia stage, interventions need to be focused on immediate symptom relief [3]. In this phase of the disease, exercise and nutritional interventions will probably not be of major importance in improving performance status or QoL. Still, for many patients it is, even in this phase, important to keep up with daily routines as long as possible, and some find comfort in being helped to maintain a certain level of physical activity and to be served small quantities of food. However, it is important that the patient does not feel pressured to do so.

In this narrative review, we have focused on nutrition and exercise interventions as part of multimodal approaches in patients with cancer at risk for losing weight. We have selectively not included and discussed studies on weight reduction in cancer, post-treatment rehabilitation programs, or post-/preoperative interventions (prenutrition, mobilization, "enhanced recovery after surgery" programs). Discussing the effects of invasive artificial nutrition (tube feeding and PN) in advanced cancer we consider beyond the scope of this review.

Conclusion

To our knowledge, studies investigating combinations of several interventions in patients with active cancer and at risk for losing weight are too few and too heterogeneous to enable firm conclusions about effect, or even the optimal dose or timing. However, data presented in this review may indicate an overall benefit, especially if interventions are started before weight loss and loss of function become too severe.

References

[1] Vagnildhaug OM, Balstad TR, Almberg SS, Brunelli C, Knudsen AK, Kaasa S, et al. A cross-sectional study examining the prevalence of cachexia and areas of unmet need in patients with cancer. Support Care Cancer 2018;26:1871–80.
[2] Sun L, Quan XQ, Yu S. An epidemiological survey of cachexia in advanced cancer patients and analysis on its diagnostic and treatment status. Nutr Cancer 2015;67:1056–62.
[3] Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.
[4] Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. Eur J Cancer 2008;44:1124–32.
[5] Greig CA, Johns N, Gray C, MacDonald A, Stephens NA, Skipworth RJ, et al. Phase I/II trial of formoterol fumarate combined with megestrol acetate in cachectic patients with advanced malignancy. Support Care Cancer 2014;22:1269–75.
[6] McMillan DC, Wigmore SJ, Fearon KC, O'Gorman P, Wright CE, McArdle CS. A prospective randomized study of megestrol acetate and ibuprofen in gastrointestinal cancer patients with weight loss. Br J Cancer 1999;79:495–500.
[7] Cerchietti LC, Navigante AH, Castro MA. Effects of eicosapentaenoic and docosahexaenoic n-3 fatty acids from fish oil and preferential Cox-2 inhibition on systemic syndromes in patients with advanced lung cancer. Nutr Cancer 2007;59:14–20.
[8] Maccio A, Madeddu C, Gramignano G, Mulas C, Floris C, Sanna E, et al. A randomized phase III clinical trial of a combined treatment for cachexia in patients with gynecological cancers: evaluating the impact on metabolic and inflammatory profiles and quality of life. Gynecol Oncol 2012;124:417–25.
[9] Solheim TS, Laird BJ. Evidence base for multimodal therapy in cachexia. Curr Opin Support Palliat Care 2012;6:424–31.
[10] Balstad TR, Kaasa S, Solheim TS. Multimodal nutrition/anabolic therapy for wasting conditions. Curr Opin Clin Nutr Metab Care 2014;17:226–35.
[11] Thorne F, Baldwin C. Multimodal interventions including nutrition in the prevention and management of disease-related malnutrition in adults: a systematic review of randomised control trials. Clin Nutr 2014;33:375–84.
[12] Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, Oldervoll LM. Effect of physical exercise on muscle mass and strength in cancer patients during treatment—a systematic review. Crit Rev Oncol Hematol 2013;88:573–93.
[13] Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr 2017;36:49–64.
[14] Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition – a consensus report from the global clinical nutrition community. Clin Nutr 2019;38:1–9.

[15] Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36:11–48.
[16] Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. Clin Nutr 2017;36:1187–96.
[17] Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers 2018;4:17105.
[18] Nasrah R, Kanbalian M, Van Der Borch C, Swinton N, Wing S, Jagoe RT. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. Clin Nutr 2018;37:235–41.
[19] Vazeille C, Jouinot A, Durand JP, Neveux N, Boudou-Rouquette P, Huillard O, et al. Relation between hypermetabolism, cachexia, and survival in cancer patients: a prospective study in 390 cancer patients before initiation of anticancer therapy. Am J Clin Nutr 2017;105:1139–47.
[20] de van der Schueren MAE, Laviano A, Blanchard H, Jourdan M, Arends J, Baracos VE. Systematic review and meta-analysis of the evidence for oral nutritional intervention on nutritional and clinical outcomes during chemo(radio) therapy: current evidence and guidance for design of future trials. Ann Oncol 2018;29:1141–53.
[21] Baldwin C, Spiro A, McGough C, Norman AR, Gillbanks A, Thomas K, et al. Simple nutritional intervention in patients with advanced cancers of the gastrointestinal tract, non-small cell lung cancers or mesothelioma and weight loss receiving chemotherapy: a randomised controlled trial. J Hum Nutr Diet 2011;24:431–40.
[22] Balstad TR, Solheim TS, Strasser F, Kaasa S, Bye A. Dietary treatment of weight loss in patients with advanced cancer and cachexia: a systematic literature review. Crit Rev Oncol Hematol 2014;91:210–21.
[23] van der Werf A, Blauwhoff-Buskermolen S, Langius JA, Berkhof J, Verheul HM, de van der Schueren MA. The effect of individualized nutritional counseling on muscle mass and treatment outcome in patients with metastatic colorectal cancer undergoing chemotherapy: a randomized controlled trial protocol. BMC Cancer 2015;15:98.
[24] Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst 2012;104:371–85.
[25] Stout NL, Baima J, Swisher AK, Winters-Stone KM, Welsh J. A systematic review of exercise systematic reviews in the cancer literature (2005-2017). PM R 2017;9:S347–S84.
[26] Turner RR, Steed L, Quirk H, Greasley RU, Saxton JM, Taylor SJ, et al. Interventions for promoting habitual exercise in people living with and beyond cancer. Cochrane Database Syst Rev 2018;9:CD010192.
[27] Peddle-McIntyre CJ, Singh F, Thomas R, Newton RU, Galvao DA, Cavalheri V. Exercise training for advanced lung cancer. Cochrane Database Syst Rev 2019;2:CD012685.
[28] Cavalheri V, Granger C. Preoperative exercise training for patients with non-small cell lung cancer. Cochrane Database Syst Rev 2017;6:CD012020.
[29] Sommer MS, Staerkind MEB, Christensen J, Vibe-Petersen J, Larsen KR, Holst Pedersen J, et al. Effect of postsurgical rehabilitation programmes in patients operated for lung cancer: a systematic review and meta-analysis. J Rehabil Med 2018;50:236–45.
[30] Wiskemann J, Clauss D, Tjaden C, Hackert T, Schneider L, Ulrich CM, et al. Progressive resistance training to impact physical fitness and body weight in pancreatic cancer patients: a randomized controlled trial. Pancreas 2019;48:257–66.
[31] Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, et al. Physical exercise for cancer patients with advanced disease: a randomized controlled trial. Oncologist 2011;16:1649–57.
[32] Oberoi S, Robinson PD, Cataudella D, Culos-Reed SN, Davis H, Duong N, et al. Physical activity reduces fatigue in patients with cancer and hematopoietic stem cell transplant recipients: a systematic review and meta-analysis of randomized trials. Crit Rev Oncol Hematol 2018;122:52–9.
[33] Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck-de Leeuw IM, Courneya KS, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. Br J Sports Med 2018;52:505–13.
[34] Dittus KL, Gramling RE, Ades PA. Exercise interventions for individuals with advanced cancer: a systematic review. Prev Med 2017;104:124–32.
[35] Adamsen L, Quist M, Andersen C, Moller T, Herrstedt J, Kronborg D, et al. Effect of a multimodal high intensity exercise intervention in cancer patients undergoing chemotherapy: randomised controlled trial. BMJ 2009;339:b3410.
[36] Zimmer P, Trebing S, Timmers-Trebing U, Schenk A, Paust R, Bloch W, et al. Eight-week, multimodal exercise counteracts a progress of chemotherapy-induced peripheral neuropathy and improves balance and strength in metastasized colorectal cancer patients: a randomized controlled trial. Support Care Cancer 2018;26:615–24.
[37] Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. Med Sci Sports Exerc 2013;45:2080–90.
[38] Cheema BS, Kilbreath SL, Fahey PP, Delaney GP, Atlantis E. Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 2014;148:249–68.
[39] Jatoi A, Rowland K, Loprinzi CL, Sloan JA, Dakhil SR, MacDonald N, et al. An eicosapentaenoic acid supplement versus megestrol acetate versus both for patients with cancer-associated wasting: a North Central Cancer Treatment Group and National Cancer Institute of Canada collaborative effort. J Clin Oncol 2004;22:2469–76.
[40] Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, Dakhil SR, Mailliard JA, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol 2002;20:567–73.
[41] Mantovani G, Maccio A, Madeddu C, Serpe R, Massa E, Dessi M, et al. Randomized phase III clinical trial of five different arms of treatment in 332 patients with cancer cachexia. Oncologist 2010;15:200–11.
[42] Madeddu C, Dessi M, Panzone F, Serpe R, Antoni G, Cau MC, et al. Randomized phase III clinical trial of a combined treatment with carnitine + celecoxib +/- megestrol acetate for patients with cancer-related anorexia/cachexia syndrome. Clin Nutr 2012;31:176–82.
[43] Mantovani G. Randomised phase III clinical trial of 5 different arms of treatment on 332 patients with cancer cachexia. Eur Rev Med Pharmacol Sci 2010;14:292–301.
[44] Daneryd P, Svanberg E, Korner U, Lindholm E, Sandstrom R, Brevinge H, et al. Protection of metabolic and exercise capacity in unselected weight-losing cancer patients following treatment with recombinant erythropoietin: a randomized prospective study. Cancer Res 1998;58:5374–9.
[45] Sandmael JA, Bye A, Solheim TS, Stene GB, Thorsen L, Kaasa S, et al. Feasibility and preliminary effects of resistance training and nutritional supplements during versus after radiotherapy in patients with head and neck cancer: a pilot randomized trial. Cancer 2017;123:4440–8.
[46] Lonbro S, Dalgas U, Primdahl H, Overgaard J, Overgaard K. Feasibility and efficacy of progressive resistance training and dietary supplements in radiotherapy treated head and neck cancer patients—the DAHANCA 25 A study. Acta Oncol 2013;52:310–8.
[47] Uster A, Ruehlin M, Mey S, Gisi D, Knols R, Imoberdorf R, et al. Effects of nutrition and physical exercise intervention in palliative cancer patients: a randomized controlled trial. Clin Nutr 2018;37:1202–9.
[48] Naito T, Mitsunaga S, Miura S, Tatematsu N, Inano T, Mouri T, et al. Feasibility of early multimodal interventions for elderly patients with advanced pancreatic and non-small-cell lung cancer. J Cachexia Sarcopenia Muscle 2018;10:73–83.
[49] Lundholm K, Daneryd P, Bosaeus I, Korner U, Lindholm E. Palliative nutritional intervention in addition to cyclooxygenase and erythropoietin treatment for patients with malignant disease: effects on survival, metabolism, and function. Cancer 2004;100:1967–77.
[50] Lundholm K, Korner U, Gunnebo L, Sixt-Ammilon P, Fouladiun M, Daneryd P, et al. Insulin treatment in cancer cachexia: effects on survival, metabolism, and physical functioning. Clin Cancer Res 2007;13:2699–706.
[51] Solheim TS, Laird BJA, Balstad TR, Stene GB, Bye A, Johns N, et al. A randomized phase II feasibility trial of a multimodal intervention for the management of cachexia in lung and pancreatic cancer. J Cachexia Sarcopenia Muscle 2017;8:778–88.
[52] Solheim TS, Laird BJA, Balstad TR, Bye A, Stene G, Baracos V, et al. Cancer cachexia: rationale for the MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial. BMJ Support Palliat Care 2018;8:258–65.
[53] Cerchietti LC, Navigante AH, Peluffo GD, Diament MJ, Stillitani I, Klein SA, et al. Effects of celecoxib, medroxyprogesterone, and dietary intervention on systemic syndromes in patients with advanced lung adenocarcinoma: a pilot study. J Pain Symptom Manage 2004;27:85–95.
[54] Gagnon B, Murphy J, Eades M, Lemoignan J, Jelowicki M, Carney S, et al. A prospective evaluation of an interdisciplinary nutrition-rehabilitation program for patients with advanced cancer. Curr Oncol 2013;20:310–8.
[55] Parmar MP, Swanson T, Jagoe RT. Weight changes correlate with alterations in subjective physical function in advanced cancer patients referred to a specialized nutrition and rehabilitation team. Support Care Cancer 2013;21:2049–57.
[56] Parmar MP, Vanderbyl BL, Kanbalian M, Windholz TY, Tran AT, Jagoe RT. A multidisciplinary rehabilitation programme for cancer cachexia improves quality of life. BMJ Support Palliat Care 2017;7:441–9.
[57] Del Fabbro E, Hui D, Dalal S, Dev R, Nooruddin ZI, Bruera E. Clinical outcomes and contributors to weight loss in a cancer cachexia clinic. J Palliat Med 2011;14:1004–8.
[58] Ruiz-Garcia V, Lopez-Briz E, Carbonell-Sanchis R, Bort-Marti S, Gonzalvez-Perales JL. Megestrol acetate for cachexia-anorexia syndrome. A systematic review. J Cachexia Sarcopenia Muscle 2018;9:444–52.
[59] Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol 2005;23:8500–11.