cases of thromboembolic/thrombotic disease, heart disease, or for patients at risk for serious fluid retention [104].

Although the mechanism of weight gain of progestational drugs in presently uncertain, it might be related to glucocorticoid activity [105]. MA may induce appetite via stimulation of NPY, a potent central appetite stimulant in the hypothalamus, modulation of calcium channels in the ventromedial hypothalamus (VMH)—a well known satiety center [1, 4, 125–133] which reduces the firing tone of VMH neurons. On the other hand, MPA has been shown to inhibit the activity of proinflammatory cytokines such as IL-1, IL-6, and TNF-α [28, 109, 134]. Serum levels of such cytokines were reported to be decreased in cancer patients after MA or MPA treatment [109]. More studies are needed to finally clarify the pharmacologic effects of MA and MPA drugs and to confirm the anti-inflammatory effects.

Several other drugs have been evaluated as agents to ameliorate cancer anorexia-cachexia. Corticosteroids are frequently used in clinical practice for appetite stimulation in patients with advanced malignancies and randomized clinical trials showed that corticosteroid medications may stimulate appetites in patients with advanced cancer [135]. However, these studies were not able to show any substantial non-fluid weight gain in treated patients [135]. Efforts are also ongoing to evaluate both anabolic steroids and hydrazine sulfate as drugs for the treatment of patients with cancer cachexia [135].

Hydrazine is a substance that inhibits the enzyme phosphoenol pyruvate carboxykinase (PEP-CK) and interferes with gluconeogenesis [135]. However, hydrazine and hydrazine sulfate might be a human carcinogen based on evidence for carcinogenicity in animal studies [135, 136]. The preliminary nature of these investigations, however, precludes recommendations for the use of these drugs in routine clinical practice [135].

Other orexigenic agents

The orexigenic mediator ghrelin has been reported as having a key role in increasing appetite and, therefore, food intake. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptors [137, 138]. It is synthesized principally in the stomach and is released in response to fasting [138].

Ghrelin strongly stimulates GH secretion in humans [139–142] and does so more potently than GHRH by several fold under similar circumstances [143]. Furthermore, ghrelin and GHRH synergistically increases GH release [141]. GH regulates IGF-1 levels and increases muscle strength [144, 145], whereas GH enhances lipolysis, IGF-1 stimulates protein synthesis, myoblast differentiation, and muscle growth [143]. Evidence that ghrelin exerts anti-inflammatory actions has been accumulating [143]. Ghrelin induces the anti-inflammatory cytokine IL-10 [146, 147], suppressing the production of proinflammatory cytokines, including IL-1β, IL-6, and TNF-α both in vitro [148, 149], and in vivo [146, 150, 151]. Additionally, ghrelin inhibits the activation of NF-κB, which controls the production of multiple proinflammatory cytokines during inflammatory insults [147, 149, 150]. Although the molecular mechanisms and cellular targets mediating ghrelin inhibition of NF-κB activation remain to be determined, the vagus nerve may play an important role in the ghrelin-mediated inhibition of proinflammatory cytokine release [150, 152]. MuRF1 and MAFbx are upregulated under cachectic catabolic conditions, and NF-κB activation may regulate skeletal muscle proteasome expression and protein degradation [143]. The elevations in MuRF1 and MAFbx expression seen in skeletal muscle after thermal injury, arthritis, and dexamethasone administration were normalized, attenuated, and prevented, respectively, by ghrelin or GHS administration [153–156]. IGF-1 prevents the expression of MuRF1 and MAFbx by inhibiting FoxO transcription factors via stimulation of the PI3K/Akt pathway [143]. The IGF-1 receptor triggers activation of several intracellular kinases, including PI3K [156]. Thus, the effects of ghrelin on NF-κB activation and IGF-1 synthesis are favorable for minimizing inflammatory responses and skeletal muscle wasting in patients with cachexia [143].

In addition to increasing food intake, an experimental study has shown that repeated administration of ghrelin improves cardiac structure and function, and attenuates the development of cardiac cachexia in chronic heart failure (CHF). These results suggest that ghrelin has cardiovascular effects and regulates energy metabolism through growth hormone-dependent and -independent mechanisms [157]. Thus, administration of ghrelin may be a new therapeutic strategy for the treatment of severe CHF [157].

At present, a phase II randomized, placebo-controlled, double-blind study, using an oral ghrelin mimetic, demonstrated an improvement in lean body mass, total body mass and hand grip strength in cachectic cancer patients [158]. Several clinical trials with ghrelin are currently on going.

Herbal medicine; translational aspects, particularly for cancer cachexia

There have been a number of published cases of cancer patients treated with Kampo, a form of Japanese traditional herbal medical practice, who reportedly experienced significant clinical benefits [159]. As an example, *rikkunshito*, a Kampo formula, has been shown to be useful in clinical practice for cachectic cancer patients.

Rikkunshito has been used to treat gastrointestinal tract disorders such as functional dyspepsia [160–164] and

gastroesophageal reflux [165]. A recent study regarding the underlying mechanisms of *rikkunshito* has shown that *rikkunshito* and its component 10-gingerol may inhibit the degradation of acyl-ghrelin by inhibiting the circulating ghrelin degrading enzyme [166]. Another study has shown that administration of *rikkunshito* reversed the decrease in hypothalamic ghrelin secretion and food intake 24 h after cisplatin treatment [6]. A most recent study showed that *rikkunshito* improved anorexia, gastrointestinal dysmotility, muscle wasting, and anxiety-related behavior [10]. In this study, *rikkunshito* in tumor-bearing rats was effective not only against anorexia–cachexia, but also for promoting survival, particularly in combination with chemotherapy [10]. Moreover, median survival of pancreatic cancer patients with ascites who were treated with gemcitabine was significantly prolonged by administration of *rikkunshito* [10]. Active components of *rikkunshito*, *hesperidin* and *atractylodin*, potentiated ghrelin secretion and receptor signaling, respectively, and *atractylodin* prolonged survival in tumor-bearing rats [10]. The physiological functions of endogenous ghrelin are enhanced by the dual actions of rikkunshito; which involve the stimulation of ghrelin secretion and the activation of GHS-R activity, possibly due to allosteric changes in the receptor [10]. These studies suggest that *rikkunshito* may be useful in clinical practice for cachectic cancer patients.

Because Japanese Kampo has long been used, the potential risks and benefits of its use are well recognized despite the relative paucity of the mechanistic insights [159]. Unconventional therapies such as herbs and minerals that have been used in ancient medical traditions have led to the identification of active anticancer agents [159]. Although the working mechanisms of some of the herbs and minerals are unclear and remain to be elucidated, they are worth further studying as newly potential therapy agents for cancer treatment [167].

Non pharmacological treatments

Diet modification

Because cancer cachexia differs from starvation, to date, single modality therapies with traditional nutritional regimens have failed to demonstrate efficacy in improving weight gain, including a gain in lean body mass, in patients diagnosed with cancer cachexia [168]. The average caloric deficit in weight-losing patients with cancer cachexia is approximately 250–400 kcals/day [168]. An average supplementation of 1 calorie/mL has not been shown to improve the nutritional status of patients receiving chemotherapy [169, 170]. However, recent studies using a more calorie- protein-dense supplementation have suggested that weight stabilization can be achieved; however, improvements in lean body mass has not yet been observed [171].

Patients with cancer cachexia undergoing aggressive re-feeding are at risk for 're-feeding syndrome' during the first 2–3 weeks of treatment [172]. This potentially lethal condition is characterized by severe electrolyte and fluid shifts due to metabolic abnormalities and bears a significant risk for morbidity and mortality [172]. The clinical features include fluid-balance disturbances, abnormal glucose metabolism, hypophosphatemia, hypomagnesiemia, and hypokalemia [173].

Before starting the re-feeding process, electrolyte disorders should be corrected and circulatory volume should be carefully restored. This may delay the administration of complete nutrition but is usually accomplished within 12–24 h. Caloric repletion should be at a slow rate of approximately 20 kcal/kg per day (or 1000 kcal per day) initially. However this rate may not meet the patients' fluid, sodium, potassium, protein, or vitamin requirements unless these are specifically addressed.

Gradual introduction of calories, particularly over the first week of re-feeding, should be prudent until the patient is metabolically stable [174]. Hypophosphatemia has to be treated if the serum level is less than 0.30 mmol/l or the patient is symptomatic. Supplementation of phosphate should be given intravenously at 40–80 mmol/day, together with magnesium (8–16 mmol/day) and potassium (80–120 mmol per day). These dosages should be adjusted according to monitored serum levels [175].

Exercise

Physical exercise may be beneficial in the treatment of cancer cachexia, as it increases insulin sensitivity, protein synthesis rate, and anti-oxidative enzyme activity [97]. It also may lead to a suppression of the inflammatory response and an enhancement of immune function [176]. All of these mechanisms can help to curb the pathophysiological changes underlying cachexia.

There is significant evidence that endurance exercise (e.g., high number of repetitions performed over extended time periods against relatively low resistance) ameliorates cancer-related fatigue [177]. By contrast, resistance exercise (lower number of repetitions against higher resistance) attenuates muscle wasting in different catabolic conditions [97]. Physical therapy is also advised during periods of bed rest, as reduced fitness, strength, and loss of lean body mass may occur [178]. Physical therapy can help to counteract fatigue and depression, as well as maintain strength and range of motion [97].

Although it is increasingly recognized that exercise training seems to be a polypill against the dramatic changes in the skeletal muscle in cachexia, scientific proof is scarce

[97]. As a matter of fact, there are only very few clinical trials investigating the impact of exercise training in cachexia [97]. A few small studies have shown that exercise training leads to changes in body composition [97]. Investigations with larger cohorts and hard end points are still missing [97]. Most of the research concerning exercise training and cachexia has been done in the field of cancer cachexia, preferably with animal models [97]. It is still under discussion as to which patients with refractory cachexia might profit from mild physical activity intervention [97]. Counseling patients on cancer-related fatigue can encourage patients to maintain a minimal form of activity and slow down the decrease in physical function and quality of life [97].

Nutritional counseling

The management of cachexia in advanced cancer patients should focus on maximizing oral intake by allowing the patient flexibility in type, quantity, and timing of meals [99]. Nutritional counseling has been reported to improve nutritional intake in patients undergoing chemotherapy [179]. Moreover, it has also been shown to improve quality of life in patients undergoing radiotherapy [180]. However, the influence of counseling on reducing psychological distress in patients with a palliative care setting remains to be established [97].

Adequate education and counseling should also address the concerns of family members who may worry that their relative appears to be 'starving to death' by underscoring the differences between starvation and cachexia [97]. The appropriate provision of counseling, for example dietetic consultation or information sheet has not been established for patients with refractory cachexia [97]. Professional health care teams of oncology physicians, nurses, and dietitians can diagnose specific needs and plan individualized treatment for improved nutritional health with patients and their families [97]. Counseling, which any member of the health care team may provide, is an effective and inexpensive intervention and should be combined with other nutritional interventions [181]. Nursing interventions to counteract cachexia should be aimed at minimizing the negative factors of nausea, vomiting, diarrhea, pain, fatigue, changes in taste or food preferences that may influence appetite [99].

Even if there is no evidence that nutritional counseling improves overall quality of life or physical functioning in patients with refractory cancer cachexia, there is a strong support by experts that nutritional counseling can aid cancer patients and family members to understand the changes, and to differentiate what they can improve and where the limitations of nutrition [97, 181]. However this requires advanced psychological and nutritional knowledge on the part of the counselors [97].

Palliative care and mental health support

The health care team should ensure that patients' physical symptoms (e.g., pain, fatigue, breathlessness) are being assessed and managed effectively, as this may improve appetite, ability to take up food, and general well-being [97]. Psychological distress and psychiatric disorders are common among patients with cancer and have a prevalence ranging from 10 to 79 % [99]. These problems are also as common among the family members of people with cancer [99]. Anorexia and cachexia may result in secondary depression, or depression itself may be a prime contributor to anorexia and subsequent weight loss. Benzodiazepines can be helpful for persistent fear and anxiety, and antidepressant drugs are increasingly used in patients with cancer with comorbid depression [99].

The use of psychological and behavioral interventions (e.g., relaxation, hypnosis, and short-term group psychotherapy) in cancer is increasing and recent studies have suggested that some of these techniques may affect quality of life and, perhaps, survival rates [99]. However, there is no evidence that psychotherapeutic interventions have an effect on nutritional status [97]. Moreover, for refractory cachexia, reduced performance status and short prognosis may preclude this intervention [97].

Caring for a person with advanced disease can be physically and emotionally stressful [97]. Caregivers often note that when friction occurs between themselves and the individual for whom they are caring, it often occurs over the issue of eating [99]. These caregivers report that they find it hard to cope with the patient who relentlessly loses weight and strength and yet persistently refuses adequate food intake [99]. Effective communication with patients and their families is essential and is an important component of treatment [99].

Managing side effects

Many cancer interventions will exacerbate already reduced energy and nutrient intake [80]. Surgical patients may be fasted for prolonged periods peri-operatively, and both chemotherapy and radiotherapy can induce side-effects such as anorexia, nausea, vomiting, mucositis, taste change, or lethargy [80]. Symptoms will depend on the nature and course of the chemotherapeutic drugs being used and the location, volume, and dose of radiotherapy [80]. Some cytotoxic drugs may even generate their own cachexia-like side-effects [82]. For example, antitubulin taxanes induce greater loss of body weight in tumor-bearing mice than in healthy mice, even when the agents significantly reduce tumor growth [80]. The complex interaction between nutrition, cachexia, and chemotherapy still requires elucidation [80, 182, 183].

Adverse Effects of Chemotherapy and Radiation

Although chemotherapy and radiation treatments are usually directed by a subspecialist, the physician must be aware of potential adverse effects and, in some practice settings, may be called on to manage them [184].

Approximately 70–80 % of patients treated with chemotherapy experience nausea and vomiting [185], which may be acute (occurring within a few hours after chemotherapy), delayed (occurring 24 or more hours after chemotherapy), breakthrough or refractory (occurring despite prophylactic treatment), or anticipatory (occurring before chemotherapy treatment). The emetogenic (vomit-inducing) potential of chemotherapeutic agents varies from mild to severe [186]. Drug dose, schedule and route of administration, and patient variability are also factors [184].

Antiemetic therapy is most effective if given before chemotherapy and maintained while the emetic potential of the agent continues. Oral formulations are as effective as parenteral or rectal routes if the patient is able to swallow and digest tablets. Lorazepam, metoclopramide, and prochlorperazine often are used for moderate- to low emetic-risk chemotherapy and for breakthrough nausea.

Currently, 5-HT antagonists (ondansetron, granisetron, dolasetron and palonosetron) are most widely used in practice for patients given chemotherapy with a moderate-to-high risk of gastrointestinal side effects. Trials with these agents indicate that they are highly effective in controlling acute nausea and vomiting associated with chemotherapy and have minimal adverse effects [187–189]. They are equally effective for acute nausea [190], but palonosetron, which has a much higher affinity for the 5-HT receptor and a longer half-life than the other 5-HT antagonists, is more effective than dolasetron in preventing delayed emesis [191]. The co-administration of dexamethasone improves the effectiveness of 5-HT antagonists in controlling acute emesis. However, one study found that adding a 5-HT antagonist to dexamethasone for the treatment of delayed nausea and vomiting did not result in an improved antiemetic effect over dexamethasone alone [184, 192]. Aprepitant, the first neurokinin-1 receptor antagonist, augments the activity of 5-HT antagonists and dexamethasone to inhibit acute and delayed emesis induced by cisplatin [184, 193, 194].

Nausea and vomiting can also occur following radiation treatment and are most likely in patients undergoing whole body or upper abdominal radiation [184]. Higher total dose of radiation, larger amount of tissue radiated, and a higher daily fraction of radiation are also factors in the severity of nausea and vomiting [184].

Fever and neutropenia in a patient undergoing chemotherapy are also common and should be treated promptly [184]. Fever in a patient undergoing chemotherapy is common and worrisome [184]. In the guidelines developed by the Infectious Diseases Society of America (IDSA) [195], fever is defined as a single oral temperature higher than 100.9 °F (38.3 °C) or an oral temperature of 100.4 °F (38.0 °C) or higher for more than 1 h.

An absolute neutrophil count less than 500 per mm^3 (0.5 × 109 per L) is defined as severe neutropenia. The severity of infection is inversely related to the neutrophil count, with the greatest risk of bacteremia at absolute neutrophil levels lower than 100 per mm^3 (0.1 × 109 per L) [196]. Evaluation of the patient with neutropenia includes physical examination (with attention to indwelling vascular access devices), laboratory data, radiographs, and blood and urine cultures.

No single antibiotic or antibiotic combination can be uniformly recommended for all febrile neutropenic patients [184]. Initial therapy is selected after considering the most likely potential infecting organism, site of infection, organ function (e.g., kidney, liver), medication allergies, and recent antibiotic treatment [184].

The most widely used outpatient antibiotic choice is an oral fluoroquinolone or amoxicillin/clavulanate [184]. Commonly used empiric intravenous antibiotic monotherapies include carbapenems (e.g., imipenem/cilastatin, meropenem), and extended-spectrum antipseudomonal cephalosporins (e.g., ceftazidime, cefepime). Dual therapy agents include an aminoglycoside with antipseudomonal penicillin (with or without a betalactamase inhibitor) or an extended-spectrum antipseudomonal cephalosporin; and ciprofloxacin with antipseudomonal penicillin [184].

According to IDSA and National Comprehensive Cancer Network guidelines, diagnostic reassessment should occur if fever does not improve in 3–4 days [195]. Although most patients with cancer-related febrile neutropenia will recover without major complications, involvement of a subspecialist should be considered when the patient's fever does not improve after 3 or 4 days of appropriate antimicrobial treatment or when the patient has septic shock, methicillin-resistant *Staphylococcus aureus* infection, or signs and symptoms of invasive fungal infection [184].

Cancer cachexia in special populations

Elderly

The management of cancer in the older person is an increasingly common problem, as 60 % of all neoplasms occur in individuals age 65 and older [197]. Cachexia is one of the major causes of weight loss in the elderly and numerous studies have shown that weight loss is associated with an increase in mortality [198–201]. Although body weight is easily measured, the evaluation of unintended

weight loss in long-term care facilities is difficult [202]. Whether anorexia and weight loss are reversible or unavoidable requires a careful clinical evaluation in the individual patient [203]. A structured approach to the differential diagnosis of malnutrition in long-term care was developed by the Council for Nutritional Clinical Strategies in Long- Term Care [203].

Additionally, muscle mass loss is characteristic of physical frailty and sarcopenia (age-related loss of muscle mass). Physical frailty has been characterized as a condition that results from reduced strength, reduced gait velocity, reduced physical activity, weight loss, and exhaustion. Thus, sarcopenia and frailty could be classified as cachectic conditions because they are associated with muscle mass loss.

Treating weight loss in the elderly can ameliorate many medical conditions. For example, rehabilitation time following post-hip fractures has been shown to decrease with nutritional supplementation [204]. In hospitalised geriatric patients, nutritional supplementation resulted in improvement in serum protein and, nutritional status, and decreased mortality [205]. In a subset of geriatric inpatients, low serum albumin with weight loss predicts those patients at highest risk for dying during the subsequent 2 years [206].

Moreover, in elderly patients with cachexia, medical, cognitive, and psychiatric disorders may diminish self-sufficiency in activities of daily living (e.g., grooming, ambulation), thus reducing health-related quality of life and increasing the frequency of secondary procedures, hospitalizations, and need for skilled nursing care [198, 199]. Increased understanding of the pathophysiology of geriatric cachexia in geriatric patients has resulted in effective and safe nutritional measures [206]. In particular, a better understanding of the role of proinflammatory cytokines (e.g., increased levels of negative regulatory cytokines) in cancer cachexia in the elderly may lead to pharmacological treatment targeted for this population [207].

The potential involvement of IL-6, TNF-α, IL-1, serotonin, PGE2 and other cytokines (e.g., IL-10, IL-4, IL-15) in the pathophysiology of aging, chronic diseases, and wasting calls for additional research on ways to suppress the secretion, dysregulation, or downstream effects of the pharmacotherapy for the treatment of cachexia in elderly [207]. Further investigation with specific nutritional manipulations, and the administration of specific steroids, neuropeptides, and peptide hormones is necessary [207].

Children

Anorexia and cachexia is commonly seen in pediatric patients that receive cancer treatment. The most prominent clinical feature of cachexia in children is growth failure [97], and weight loss or decreased growth are valuable indicators of malnutrition [208]. Growth is important for children because it is an essential feature of their health [208, 209]. However, criteria for weight loss or decreased growth have seldom been used in the assessment of nutritional status in children with cancer [208]. To date, weight loss is mainly described in the literature concerning failure to thrive [210, 211], but not for describing malnutrition [208].

Children appear to be at greater nutritional risk than adults because of high protein and energy requirements and limited caloric reserves [212]. Malnutrition is associated with an increased rate of infection in children with malignant neoplasms [212].

Given the increasing attention to evidence suggesting the negative impact of cachexia on the quality of life of children with cancer, it is necessary to develop a scale that targets the concerns of pediatric patients with cancer that is specific to anorexia and cachexia [212]. An appropriate scale must have sound psychometric properties, be user friendly, and monitor cachexia-related effects on quality of life over time [212].

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