GLOBAL HEALTH

Supportive Care: Low Cost, High Value

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Overview

Supportive care aims to prevent and manage adverse effects of cancer and its treatment across the entire disease continuum. Research and clinical experience in dedicated centers have demonstrated that early appropriate supportive care interventions improve symptoms, quality of life, and overall survival in a cost-effective manner. The challenge is to assess symptoms and needs with validated tools regularly and, ideally, between clinic appointments; electronic patient-reported outcome measures and dedicated easily accessible supportive care units can help. As management of certain problems improves, others come to the fore. Cancer-related fatigue and malnutrition are very frequent and need regular screening, assessment of treatable causes, and early intervention to improve. Pharmacologic agents and phytopharmaceuticals are of little use, but other interventions are valuable: physical exercise, counseling on fatigue, and cognitive behavioral therapy/mind-body interventions (e.g., for fatigue). Nutrition should be oral, rich in proteins, and accompanied by muscle training adapted to the patient's condition. Psychological and societal counseling is often useful; nausea or other problems such as gastrointestinal dysmotility or metabolic derangements must be tackled. Chemotherapy-induced peripheral neuropathy frequently worsens quality of life and has no established prevention strategy (notwithstanding current interest in cryotherapy and compression therapy) and thus requires careful assessment of patient predisposition to develop it with the consideration of feasible dose and treatment alternatives. When painful, duloxetine helps. Nonpharmacologic strategies, including acupuncture, physical exercise, cryotherapy/compression, and scrambler therapy, are promising but require large phase III trials to become the accepted standard. Personalization of chemotherapy, dependent on realistic goals, is key.

EARLY AND APPROPRIATE INTEGRATION OF SUPPORTIVE CARE IN TREATMENT OF PATIENTS WITH CANCER

The Multinational Association of Supportive Care in Cancer definition of supportive care highlights "the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to post-treatment care. Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to supportive care."[1] In 2012, ASCO was the first oncology society to publish a clinical opinion on integration of palliative care in oncology, to then update and establish it,[2] and to develop a global resource-stratified guideline.[3] The European Society for Medical Oncology (ESMO) has also stated in 2014 that oncologists should be committed to preserving the quality of life of patients with cancer through the entire "cancer journey," including optimal supportive care.[4] In a more recent position paper on supportive and palliative care,[5] ESMO has suggested that the term "patient-centered care" be used to cover both supportive and palliative care approaches during the continuum of cancer illness, with regular multidisciplinary team assessments of patients' needs, which vary and evolve over time. Multiple possible assessments and interventions tailored to cancer-related symptoms and toxicities of anticancer treatments are listed, including appropriate prevention and training goals agreed in the ESMO/ASCO curriculum.

A cancer pandemic has been triggered by the COVID-19 crisis, leading to delayed diagnoses and initiations of treatment that will have a staggering cost in human lives.[6] Thus far not quantified is the impact of the COVID-19 pandemic on quality of treatment and supportive care for patients with cancer. New barriers to access to cancer specialists, clinics, and hospitals, perceived or real, mean that many patients may have unnecessary symptoms caused by disease or toxicity of oncologic treatments. Unfortunately, this comes at a time when it has been established beyond doubt that appropriate timely supportive care interventions improve symptom burden, performance status, overall management costs, and survival.

Basch et al[7] used electronic patient-reported outcome measures systematically to monitor patients' symptoms and to detect problems earlier. Through early intervention, this led to improved symptom management, decreased symptom severity and number of hospitalizations or emergency room visits, and increased survival, probably through more time on effective therapy.[8]

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Accepted on February 22, 2021 and published at ascopubs.org on April 8, 2021: DOI https://doi.org/10.1200/EDBK_320041

PRACTICAL APPLICATIONS

- The "cancer pandemic" caused by the COVID-19 crisis raised obstacles for patients to be treated in a timely fashion but also to reach appropriate and early supportive care.
- Regular symptoms-monitoring using digital patient-reported outcome measures or dedicated supportive care units facilitating information access and management of symptoms will improve symptom burden, performance status, overall management costs, and survival.
- Cancer-related fatigue is among the most distressing issues for patients with cancer and should be approached mainly with non-pharmacologic interventions.
- Nausea and other risks of malnutrition require close attention and multiprofessional care.
- Neuropathy symptoms must be monitored, and dose reductions/modifications should be considered based on functional status.

Concurrently, patients with lung cancer after initial treatment were randomly assigned in five French centers[9] to either receive routine clinical and CT scan follow-up or web-guided follow-up. In this latter group, weekly patient-scored symptoms triggered an alert when predefined criteria were met. In the experimental arm, progression was spotted earlier, and performance status had not yet significantly deteriorated in a higher proportion of patients who were thus able to receive optimal treatment, leading to a 7-month improvement in overall survival that increased with longer follow-up.[10]

VARIOUS MODELS OF EARLY SUPPORTIVE CARE IMPLEMENTATION HAVE BEEN DEVELOPED

One strategy is regular digital monitoring and management of symptoms and needs using regular electronic patient-reported outcome measures, as pioneered by the above-discussed trials, with data being evaluated by the cancer professionals treating the patients, often primarily led by experienced nurses.[11] This approach has the advantage of picking up deteriorations in overall well-being between scheduled clinic visits and potentially predicting toxicity, with high patient and health care provider satisfaction with improved workflow in oncology units and time savings by reduction of phone calls and emergency visits.[12] Modern digital health monitoring apps allow both an overview of all patients in the program within the last week (Fig. 1) and of symptoms development in given patients over time. Given the wide availability of smartphones, even in low-income countries in which primary care structures may be weak and access to specialist care constrained, such follow-up strategies, possibly automated, may greatly improve outcomes.

Another strategy developed in many cancer centers worldwide is the establishment of ambulatory and inpatient supportive care units that grant patients low-barrier access to expertise in supportive care while at the same time minimizing disruption to acute oncology clinics. The Multinational Association of Supportive Care in Cancer has begun to certify centers of excellence in supportive care in cancer that apply this principle to optimize supportive care along the whole disease trajectory.[13]

Finally, successful models of supportive care implementation are promoted by national supportive care societies, such as those of France (Association Francophone des Soins Oncologiques de Support), Italy (Network Italiano Cure di Supporto in Oncologia), Russia (Russian Society of Supportive Care in Oncology), India (Indian Association of Supportive Care in Cancer), and Japan (Japanese Association of Supportive Care in Cancer). In the United Kingdom, the "enhanced supportive care" program initiated by Dr. Richard Berman, consultant in palliative care at the Christie Hospital, was so successful regarding earlier referral of patients with supportive care needs, improved symptom control, improved quality of life, improved overall survival, and reduced health care costs that the National Health Service in the United Kingdom supported its implementation in 21 cancer centers across the United Kingdom.[14] The key steps in achieving this feat in the United Kingdom are summarized in this guidance document.[15]

As availability and quality of supportive and palliative care have improved, there have been vast shifts in symptoms and toxicities most feared by patients and their families.[16] A classic example is the fear of vomiting with highly emetogenic chemotherapy; this was once a nearly universal occurrence. Advances in understanding emesis mechanisms, an early report,[17] and rigorous trials that established 5-HT3 antagonists as standard in nausea and vomiting led to recognition of this supportive care breakthrough as one of ASCO's top five advances in 50 years.[18] Incorporation of neurokinin 1 receptor antagonists and olanzapine in strategies to optimize antiemetic efficacy[19] has further improved nausea and vomiting control, the latter drug also being cheap and widely available. However, adherence to guidelines for prevention of nausea and vomiting is still low in certain settings,[20] and nonadherence is associated with avoidable acute health care use and costs.[21]

High-quality guidelines exist for most supportive care topics. Table 1[2,3,22-44] provides an overview of selected guidelines, as well as the ASCO guidelines (www.asco.org/research-guidelines/quality-guidelines/guidelines/supportive-care-and-treatment-related-issues%20), ESMO guidelines (www.esmo.org/guidelines/supportive-and-palliative-care), and National

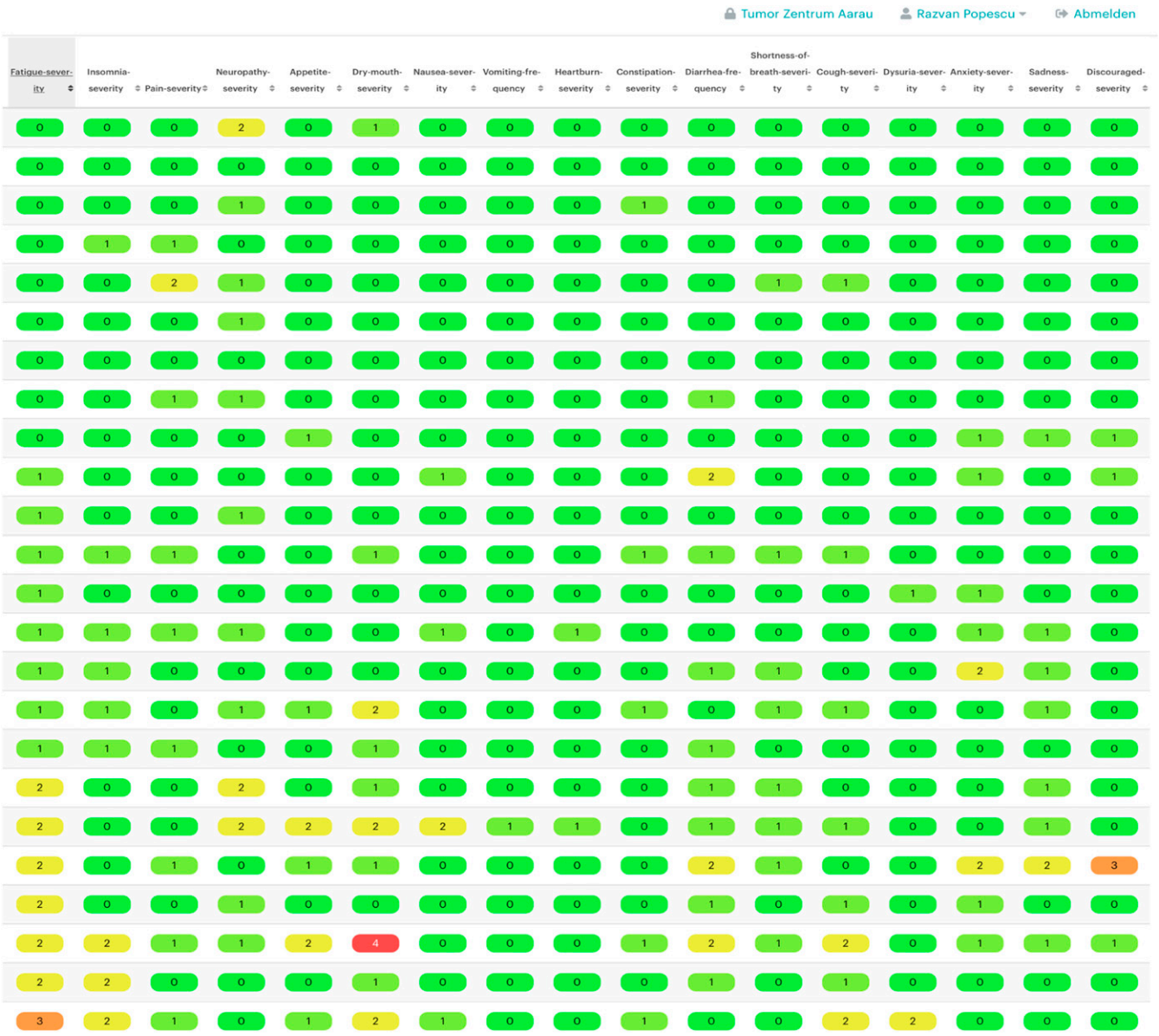

FIGURE 1. Bird's-Eye View of Symptoms for Patients Replying to a Chemotherapy Questionnaire in the Last 2 Weeks
Symptoms are sorted by ascending fatigue severity. Each line represents a patient, and each column represents a symptom.

Comprehensive Cancer Network recommendations (www.nccn.org/professionals/physician_gls/default.aspx#supportive).

This 2021 ASCO Annual Meeting educational session this article is based on will further focus on three major symptoms that are leading current symptoms and toxicities lists and on where appropriate intervention (or refraining from therapies with unproven benefit) may greatly improve the well-being of patients with cancer.

EXHAUSTED: DEALING WITH FATIGUE

Cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment. Cancer-related fatigue is not proportional to recent physical activity and interferes with usual functioning. In comparison with the fatigue experienced by healthy individuals, fatigue related to cancer is seldom alleviated by rest or sleep.[24,26,45]

Cancer-related fatigue is reported by 60% to 65% of patients and can occur at any time for patients with cancer, before, during, and even long after the completion of antineoplastic treatment. Cancer-related fatigue occurs in up to 40% of patients at diagnosis, 80% and 90% of patients during chemotherapy and radiotherapy, respectively, and

TABLE 1. Overview of Selected Supportive Care Guidelines From ASCO, the European Society for Medical Oncology, the Multinational Association of Supportive Care in Cancer, and the European Society for Clinical Nutrition and Metabolism

Symptom/Toxicity	ASCO [First Author, Reference (Year)]	ESMO [First Author, Reference (Year)]	MASCC [First Author, Reference (Year)]	General Recommendations
Nausea and vomiting	Hesketh et al[22] (2020)	Roila et al[23] (2016)	Roila et al[23] (2016)	Determine prevention and rescue options for antiemetics based on emetogenic potential of agent, alleviate fear and pain, and advise on sensible food choices
Nutrition/cancer/cachexia	Bower et al[24] (2014)		Arends et al[25] (2017)	Screen regularly, offer dietary counseling, avoid routine enteral/parenteral feeding; insufficient evidence to strongly endorse pharmacologic interventions
Fatigue	Bower et al[24] (2014)	Fabi et al[26] (2020)		Screen regularly, promising nonpharmacologic interventions
Neuropathy	Loprinzi et al[27] (2020)	Jordan et al[28] (2020)		No prevention strategy; duloxetine only proven pharmacologic strategy
Mucositis		Peterson et al[29] (2011)	Elad et al[30] (2020)	Routine oral care, oral cryotherapy, recombinant human keratinocyte growth factor-1 (KGF-1/palifermin), and low-level laser therapy
Immune adverse events	Brahmer et al[31] (2018)	Haanen et al[32] (2017)	Rapoport et al[33] (2020)	Close monitoring and multidisciplinary management of toxicities are needed
Febrile neutropenia	Taplitz et al[34] (2018)	de Naurois et al[35] (2010)	MASCC[36] (2021)	Early antibiotics, MASCC Cancer Index for outpatient treatment
Growth factors	Smith et al[37] (2015) Bohlius et al[38] (2019)	Aapro et al[39] (2018)		Prophylactic use to reduce the risk is warranted when the risk of febrile neutropenia is approximately 20%
Diarrhea	Benson et al[40] (2004)	Bossi et al[41] (2018)		Early intervention with fluids and loperamide; aggressive interventions, including testing for infection and antibiotics
Bone health/medication-related osteonecrosis of the jaw	Yarom et al[42] (2019)	Coleman et al[43] (2014)	Yarom et al[42] (2019)	Preventive care, treatment with antimicrobial mouth rinses, antibiotics, and conservative surgical interventions
Vulnerable populations: older adults	Mohile et al[44] (2018)			Geriatric assessment for patients older than age 65 to inform recommendations for treatment
Palliative care in the global setting	Osman et al[3] (2018)			Standards for psychosocial support, spiritual support, and pain management
Integration of palliative care into oncology setting	Ferrell et al[2] (2017)			Inpatients and outpatients with advanced cancer should receive early access to palliative care

Abbreviations: ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer.

in approximately 30% to 35% of patients in the post-treatment phase.

Possible causes of cancer-related fatigue are 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and ATP metabolism, hypothalamic-pituitary-adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation.[46]

All patients with cancer should be routinely screened for the presence and severity of fatigue at their first visit and then during therapy and approximately every year in the post-treatment phase. Screening should be done using brief and validated tools with established cutoff values for severity, such as the Numerical Rating Scale and the Brief Fatigue Inventory, which integrate the assessment of fatigue severity and its impact on important functional domains. For patients who test positive for cancer-related fatigue (values of Numerical Rating Scale > 3, indicating moderate to severe fatigue), it is necessary to identify treatable contributing factors (e.g., anemia, pain, sleep dysfunction, weight loss, concomitant medications such as opioids, and type of anticancer therapies) and comorbid conditions (e.g., endocrinopathies; cardiopulmonary disorders; hepatic, renal, and neurologic dysfunctions). To do this, oncologists should address the fatigue history, perform a physical examination, evaluate the status of the malignant disease and psychological status of the patient, and ask for a minimum battery of laboratory tests.[26]

If patients refer with mild fatigue (Numerical Rating Scale ≤ 3), not interfering with activities of daily living, patients can be reassured and counseled about strategies for coping with fatigue (physical activity and energy conservation). If patients refer with moderate/severe fatigue (Numerical Rating Scale > 3) interfering with activities of daily living, the factors that contribute to cancer-related fatigue should be identified and, whenever possible, treated. Management of cancer-related fatigue can benefit from both pharmacologic and nonpharmacologic interventions.

Several randomized, double-blind, placebo-controlled studies have been carried out to evaluate the fatigue effects of various pharmacologic, phytopharmaceutic, and nutraceutic interventions. At the present time, no pharmacologic treatment has been approved by the U.S. Food and Drug Administration for the management of cancer-related fatigue.

Psychostimulants have been evaluated in 19 randomized controlled trials (11 with methylphenidate and dexmethylphenidate, four with modafinil, three with armodafinil, and one with dexamphetamine). In 15 of these trials, no superiority with respect to placebo was demonstrated, whereas four studies showed less fatigue with methylphenidate. As a result, more well-conducted studies are still necessary to define the role of psychostimulants.

Antidepressants were studied in three double-blind controlled studies (two using paroxetine and one sertraline) of patients with fatigue submitted to chemotherapy and did not demonstrate superiority with respect to placebo.

The acetylcholinesterase inhibitor donepezil was not superior to placebo in controlling fatigue.

Two double-blind studies with corticosteroids (one with dexamethasone and one with methylprednisolone administered for 7–14 days) have been carried out with patients with end-stage cancer and demonstrated superiority with respect to placebo.

Eszopiclone, a sedative hypnotic drug, and the progestinic agent megestrol acetate have not yet shown enough evidence to be recommended for cancer-related fatigue treatment.

In conclusion, all studied drugs evaluated for cancer-related fatigue, with the exception of dexamethasone and methylprednisolone for patients with terminal cancer, yielded negative results.

There is not enough evidence to support the use of either phytopharmaceutics such as American or Wisconsin ginseng (*Panax quinquefolius*) or Asian ginseng (*Panax ginseng*), guarana, mistletoe (*Viscum album*), or astragalus or nutraceutic agents such as L-carnitine, coenzyme Q_{10}, melatonin, or taurine for the management of cancer-related fatigue. In one study, Wisconsin ginseng was superior to placebo, but this study enrolled a very heterogenous cancer population (different neoplasms and different stages of disease).

Nonpharmacologic interventions have been carefully studied. The role of physical exercise for patients with cancer-related fatigue during and after active cancer treatment has been documented by multiple systematic reviews and meta-analyses. Some guidelines encourage 150 minutes of moderate aerobic exercise per week, such as fast walking, cycling, or swimming, with an additional 2 to 3 days of strength training per week, such as weightlifting, unless contraindicated (e.g., extensive lytic bone metastases, fever, or active infection).

Psychosocial interventions (e.g., information on cancer-related fatigue, its potential causes, and contributing factors) should be offered to patients with cancer. Counseling can help patients cope with fatigue (recommendations about physical activity, energy preservation, and how to delegate less important activities). Psychoeducation may be helpful for patients to identify sources of psychosocial distress and eliminate stress-producing activities whenever possible. Cognitive behavioral therapy has been demonstrated to decrease cancer-related fatigue, addressing the following factors: coping with the experience of cancer, fear

of disease recurrence, dysfunctional thoughts and beliefs regarding fatigue, sleep dysregulation, and so on.

Mindfulness-based clinical interventions combine meditation exercises with psychoeducational elements, cognitive-behavioral interventions, and movement exercises. Mindfulness-based clinical interventions in oncology demonstrated some benefits in the management of cancer-related fatigue for patients after treatment.

A Cochrane review evaluating 24 studies carried out with patients with breast cancer showed that yoga reduced cancer-related fatigue compared with no therapy. This has been confirmed recently by a systematic review including 29 randomized controlled trials. Finally, a randomized clinical trial conducted in 410 survivors of cancer showed a significant effect of yoga on cancer-related fatigue.

Several randomized controlled trials have been carried out to evaluate acupuncture for the control of cancer-related fatigue. Recently, a meta-analysis of 10 randomized clinical trials including 1,327 patients who have completed cancer treatment showed that acupuncture reduced cancer-related fatigue.

The following other mind-body interventions may offer some benefit against cancer-related fatigue, although additional studies, particularly of patients after cancer treatment, are needed: biofield therapies (touch therapy), massage, music therapy, relaxation, moxibustion (applications of heat of burning herbs on the skin), reiki, and qigong (traditional Chinese energy exercises and therapies).

NUTRITION AND NAUSEA

Weight loss occurs frequently during anticancer treatments and impacts quality of life, completion of therapies, and risk of complications. For many patients with advanced cancer, ongoing weight loss and accelerated catabolism lead to malnutrition (weight loss $>$ 5%), sarcopenia (low muscle mass, below the fifth percentile of healthy reference), and cachexia (disease-related malnutrition [i.e., weight loss worsened by activated systemic inflammation]),[47,48] with negative effects on quality of life, activities of daily living, and overall prognosis. Nausea may exhaust patients during anticancer treatment and during advanced disease, restricting quality of life and body resources.

Best supportive care regarding nutrition requires (1) early identification of patients at risk, performed most reliably using validated screening tools; (2) careful diagnosis of relevant impairments, best performed as professional assessment by trained experts; and (3) individualized targeted supportive care aiming to abolish or at least diminish symptomatic and prognostically unfavorable deficits.[25,49]

All patients with cancer should be screened every 3 to 6 months, if with stable disease, or else more frequently for the risk or presence of malnutrition. A number of validated brief questionnaire tools are available (Numerical Rating Scale 2002, Malnutrition Universal Screening Tool, Malnutrition Screening Tool, Short Nutritional Assessment Questionnaire, etc.)[50]; it is less important which tool to choose than to reliably screen all patients. Most screening tools ask for the presence of weight loss, impaired food intake, and a feeling of sickness. Further expert assessment should ask diligently for nutritional impact symptoms impairing food intake; quantify body resources (body weight and, if possible, body composition [e.g., by anthropometry, bioelectrical impedance, or CT if available]); estimate food (including protein) intake; define gastrointestinal deficits and metabolic derangements such as systemic inflammation; determine the physical activity level; and, finally, screen for the presence of chronic pain and for psychological and social distress.[25]

While designing and preparing for nutritional care, if required, expert support should be invited from gastroenterology, surgery, pain specialists, psychologists, and social workers. The first goal of nutritional care should be to enable the patient to eat normally or, if this is not possible, to offer dietary counseling to allow adequate feeding by implementing changes in food selection, food texture, meal frequency, guidance on choosing high-energy, high-protein foods, enriching foods (e.g., by adding fat/oils, protein powder), and use of oral nutritional supplements. If these measures prove inadequate, tube feeding should be offered if the lower gastrointestinal tract is working; otherwise, parenteral nutrition is the method of choice. Separate routes of feeding may be combined for optimal effect. Nutritional requirements depend on age, sex, physical activity, disease-associated metabolic rate, and other factors, but in general may be assumed as a first approximation to be per kilogram body weight and day: energy, 25 to 30 kcal; water, 30 to 40 mL; protein, 1.2 to 1.5 g; carbohydrates, 3 to 4 g; fat, 1 to 1.5 g. In tube feeding and parenteral nutrition, requirements of electrolytes, vitamins, and trace elements must be supplied daily.[25]

To antagonize catabolism of body proteins in general and muscle mass in particular, nutritional interventions for patients who are catabolic and cachectic should ensure an adequate provision of proteins (see earlier) and should always be accompanied by muscle training, best guided by a physiotherapist or exercise physiologist. Physical exercise is known to mediate anabolic and anti-inflammatory effects. In addition, to attenuate systemic inflammation, every effort should be made to prevent and rapidly treat bouts of infection, use surgical techniques minimizing metabolic stress, avoid and effectively treat all wounds, and, given the presently not clearly defined benefit-risk ratios, prudently consider symptomatic anti-inflammatory agents (e.g., corticosteroids, nonsteroidal anti-inflammatory drugs, or long-chain *n*-3 fatty acids/fish oil).[25] Several pharmacologic agents are being studied to enhance appetite, stimulate protein anabolism,

and dampen systemic inflammatory activity; the growth hormone receptor analog and appetite stimulant anamorelin recently has been approved for use in cancer cachexia in Japan,[51] whereas none of the other experimental agents have reached approval yet.

Nausea may be induced by pharmacologic agents (e.g., opioids, chemotherapy agents) and other toxins, gastrointestinal motility disorders (e.g., obstruction, stenosis, paresis), stomatitis, [hypo]pharyngeal disorders or esophagitis (e.g., radiation injury, thrush), metabolic derangements (hypercalcemia, uremia), and raised intracranial pressure (e.g., brain metastases).[52] Nausea may also result indirectly from pain, fear, or other serious psychological stressors. Fear and stress should be alleviated, and all settings that might possibly induce nausea via sight or odor should be avoided. In cases of exulcerated wounds, small bowls may be positioned (filled with coffee powder, lemon, or mint). Prevention and treatment of chemotherapy-induced nausea and vomiting should follow standard guideline recommendations, including the structured use of dexamethasone, serotonin/5-HT3 inhibitors, and the neurokinin 1 antagonist aprepitant.[22] In the palliative setting, the following agents are recommended as single agents: butyrophenones (droperidol and haloperidol) in low doses for metabolic/toxic causes; metoclopramide or domperidone for gastroparesis; diphenhydramine in case of brain metastases or in cases of accompanying hypersalivation or diarrhea; phenothiazines (promethazine, levomepromazine) are effective but should be limited to very low doses because of side effects of dizziness and sedation; and corticosteroids are effective especially in cases of brain metastases. Escalation may be achieved by combining butyrophenones and metoclopramide or metoclopramide and phenothiazines. Finally, serotonin antagonists may be added.[52] If all these efforts fail, agents may be applied intravenously with separate infusion of fluids and nutrients. A percutaneous endoscopic gastrostomy may be inserted to drain gastric fluids, and gastrointestinal secretions may be reduced effectively by parenteral somatostatin or analogs.[53]

Nutritional guidance should include conveying the importance of adequate drinking to replace fluid losses, loose clothing, keeping the head elevated, getting distracted by reading or other media, trying to carefully warm the belly, and using ginger (fresh, tea, or other).[54] Examples of practical knowledge include chewing well and slowly and drinking slowly, chewing some dry bread before rising from bed, preferring several small to few large meals, trying warm broth, preferring simple foods with few ingredients to facilitate detection of incompatibilities or aversions, preferring light foods and steaming to roasting, and trying soft foods, possibly puréed; oatmeal gruel may be helpful, as may be bitter vegetables (e.g., endive, radicchio). Fatty and spicy foods, foods with a strong aroma or smell, and flatulent foods (e.g., cabbage, legumes, onions) are best avoided.

CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Chemotherapy-induced peripheral neuropathy (CIPN) is among the most common adverse effects of chemotherapy. Symptoms can include pain, tingling, numbness, and increased temperature sensitivity. The chemotherapeutic agents most commonly associated with CIPN include paclitaxel and oxaliplatin, although this toxicity is reported with a variety of other agents, including other taxanes (docetaxel) and platinum agents (cisplatin and carboplatin), vinca alkaloids (particularly vincristine), thalidomide, carfilzomib, and bortezomib. Chemotherapy-induced peripheral neuropathy poses a global health burden worldwide; it negatively impacts survivors of cancer by reducing dose intensity of cancer treatments, can cause permanent functional impairments, and adversely affects quality of life and well-being.

The biologic mechanisms underlying neurotoxic injury that lead to clinical symptoms of CIPN are multifactorial and include inflammatory, apoptotic, and neurodegenerative pathways.[55,56] Despite the extensive research effort focused on understanding mechanisms involved in the development of CIPN, the translation of this mechanistic understanding into rationally designed, clinical intervention studies remains problematic and limited in scope.[27,28,57]

While we await improved biologic insights into CIPN, clinicians and patients continue to grapple with how to best manage this very common toxicity. The clinical prevention and management of CIPN has a number of knowledge gaps. Two recent clinical guidelines from ASCO and ESMO appraised most of these gaps.[27] According to the most recent 2020 ASCO CIPN guideline,[27] no agents can be recommended for the prevention of CIPN because of lack of high-quality evidence in general, which remains unchanged since the initial 2014 guideline. The ASCO guideline also supports duloxetine as the sole treatment option for established painful CIPN. There are insufficient data for the use of tricyclic antidepressants, gabapentinoids, or topical amitriptyline/ketamine/baclofen for treatment of CIPN, although these agents are used commonly in routine clinical practice. ESMO–European Oncology Nursing Society–European Association of Neuro-Oncology 2020 guidelines,[28] which characterized the level of evidence for the different CIPN strategies, were in agreement with ASCO and included detailed adjudication of the levels of evidence for the different strategies that are used, including various pharmacologic and nonpharmacologic approaches.

Therefore, in light of these limited levels of evidence for management of CIPN, what are patients and clinicians to do to manage this very common toxicity? One of the most important considerations includes the evaluation of fitness

for neurotoxic chemotherapy, including the presence of other comorbidities such as preexisting neuropathy, diabetes, or family hereditary neuropathy.[58] For older patients, a comprehensive geriatric assessment can evaluate the likelihood of chemotherapy's causing harm.[44] Clinicians and patients are encouraged to review together goals of care, and, if appropriate, substitution of non- or less neurotoxic regimens can be considered.

The oncology field has also recognized that there is a need to adapt the maximum tolerated dose of chemotherapy to an optimal patient-centered dose. Per ASCO 2020 guidelines, clinicians should assess and discuss with patients the appropriateness of dose delays and dose reductions for patients who are symptomatic from CIPN.[27] Dose modifications and prescription of drugs at lowest dose that produced the maximum biologic effect have been the subject of active discussion within the field and can lead to significant cost-savings and decreased toxicity.

An additional high-yield strategy for management of CIPN is to actually avoid interventions that have been shown to be of no benefit or even detrimental. For example, although the supplement industry actively markets a variety of supplements to patients undergoing cancer treatment, not one single supplement has been shown to be beneficial for the prevention or treatment of CIPN.[27] Hence, there are insufficient data to recommend any supplement per both ESMO and ASCO guidelines, and these should not be recommended as part of routine oncologic care for prevention of CIPN.[27,28]

There is currently increasing interest in nonpharmacologic strategies for prevention or treatment of CIPN because of promising early-phase studies and better tolerability. However, phase III evidence of benefit for these approaches, including acupuncture, physical exercise, cryotherapy/compression, and scrambler therapy, is not yet available, and larger clinical trials are needed to better delineate their utility.

Several studies have evaluated acupuncture therapy as a nonpharmacologic option for CIPN. One small randomized, sham-controlled trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy did not show any differences in neuropathy between groups.[59] A recent randomized controlled trial comparing 8-week acupuncture intervention with usual care led to clinically meaningful and statistically significant improvements in neuropathic sensory symptoms in survivors of breast cancer with mild and moderate CIPN.[58] Additional larger studies are needed to confirm the effect of acupuncture therapy on CIPN.

In recent years, the efficacy of cryotherapy and compression therapy to prevent taxane-induced peripheral neuropathy has been investigated by several groups. Several clinical trials also revealed that compression therapy using surgical gloves is a safe and potentially effective therapy for the amelioration of CIPN.[60,61] However, a recent study compared the efficacy of cryotherapy and compression therapy for CIPN and found no difference in incidence of CIPN using either cryotherapy or compression therapy.[62] Additional trials are ongoing to evaluate the benefits of cryotherapy, compression therapy, and/or cryo-compression therapy for prevention of CIPN.[63]

Another emerging approach is scrambler therapy for treatment of CIPN. Scrambler therapy is a cutaneous neurostimulatory treatment for the management of chronic pain syndromes and for the management of CIPN.[64] A recent randomized phase II pilot trial was conducted to evaluate the effect of scrambler therapy for treating CIPN.[65] Compared with transcutaneous electrical nerve stimulation, scrambler therapy showed at least a 50% documented improvement for patients. To confirm the effect of scrambler therapy on treatment of CIPN, larger, sham-controlled, double-blinded clinical trials are needed.

Several studies have suggested that exercise may be beneficial for other types of peripheral neuropathy. Physical exercise may attenuate CIPN through its influence on blood circulation/oxidative stress, inflammation, neurotransmitters, endogenous opioids, growth factors, neuroplasticity, and coping and symptom interaction mechanisms.[66] Several studies have shown promise in CIPN.[67-69] Additional primary studies are being planned.

Considering the debilitating consequences of CIPN on quality of life, it is imperative that shared decision-making and patient-reported outcomes are evaluated in making treatment decisions and treatment modifications for toxicity. The future development of improved, efficient intervention strategies for CIPN requires collaborative strategies that involve a multidisciplinary team of experienced pharmacologists, statisticians, and oncologists, partnered with patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_320041.

REFERENCES

1. Multinational Association of Supportive Care in Cancer. What is supportive care? https://www.mascc.org/about-mascc. Accessed February 7, 2021.
2. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35:96-112.
3. Osman H, Shrestha S, Temin S, et al. Palliative care in the global setting: ASCO Resource-Stratified Practice Guideline. J Glob Oncol. 2018;4:1-24.
4. Popescu RA, Schäfer R, Califano R, et al. The current and future role of the medical oncologist in the professional care for cancer patients: a position paper by the European Society for Medical Oncology (ESMO). Ann Oncol. 2014;25:9-15.
5. Jordan K, Aapro M, Kaasa S, et al. European Society for Medical Oncology (ESMO) position paper on supportive and palliative care. Ann Oncol. 2018;29:36-43.
6. Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020;371:m4087.
7. Basch E, Deal AM, Kris MG, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial [published correction appears in *J Clin Oncol*. 2016;34:2198]. J Clin Oncol. 2016;34:557-565.
8. Basch E, Deal AM, Dueck AC, et al. Overall survival results of a trial assessing patient-reported outcomes for symptom monitoring during routine cancer treatment. JAMA. 2017;318:197-198.
9. Denis F, Lethrosne C, Pourel N, et al. Randomized trial comparing a web-mediated follow-up with routine surveillance in lung cancer patients [published correction appears in *J Natl Cancer Inst*. 2018;110:436]. J Natl Cancer Inst. 2017;109:1-8.
10. Denis F, Basch E, Septans AL, et al. Two-year survival comparing web-based symptom monitoring vs routine surveillance following treatment for lung cancer. JAMA. 2019;321:306-307.
11. Mooney KH, Beck SL, Wong B, et al. Automated home monitoring and management of patient-reported symptoms during chemotherapy: results of the symptom care at home RCT. Cancer Med. 2017;6:537-546.
12. Schmalz O, Jacob C, Ammann J, et al. Digital monitoring and management of patients with advanced or metastatic non-small cell lung cancer treated with cancer immunotherapy and its impact on quality of clinical care: interview and survey study among health care professionals and patients. J Med Internet Res. 2020;22:e18655.
13. Multinational Association of Supportive Care in Cancer. MASCC Designated Centers of Excellence in Supportive Care in Cancer. https://www.mascc.org/mascc-designated-centers-of-excellence-in-supportive-care-in-cancer. Accessed December 7, 2020.
14. National Health Service. Thousands of cancer patients to benefit from early supportive care. https://www.england.nhs.uk/2016/07/early-supportive-care/. Accessed March 4, 2021.
15. National Health Service. Enhanced supportive care integrating supportive care in oncology. https://www.england.nhs.uk/wp-content/uploads/2016/03/ca1-enhncd-supprtv-care-guid.pdf. Accessed March 4, 2021.
16. Carelle N, Piotto E, Bellanger A, et al. Changing patient perceptions of the side effects of cancer chemotherapy. Cancer. 2002;95:155-163.
17. Leibundgut U, Lancranjan I. First results with ICS 205-930 (5-ht3 receptor antagonist) in prevention of chemotherapy-induced emesis. Lancet. 1987;329:P1198.
18. Goldberg K. ASCO 50th anniversary poll names the top 5 advances from the past 50 years. https://www.asco.org/about-asco/press-center/news-releases/asco-50th-anniversary-poll-names-top-5-advances-past-50-years. Accessed March 4, 2021.
19. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update [published correction appears in J Clin Oncol. 2018;361459]. J Clin Oncol. 2017;35:3240-3261.
20. Roeland EJ, Ruddy KJ, LeBlanc TW, et al. What the HEC? Clinician adherence to evidence-based antiemetic prophylaxis for highly emetogenic chemotherapy. J Natl Compr Canc Netw. 2020;18:676-681.
21. Navari RM, Ruddy KJ, LeBlanc TW, et al. Avoidable acute care use associated with nausea and vomiting among patients receiving highly emetogenic chemotherapy or oxaliplatin. Oncologist. Epub 2020 Dec 1.
22. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update [published corrections appear in *J Clin Oncol*. 2020;38:3825 and 2021;39:96]. J Clin Oncol. 2020;38:2782-2797.
23. Roila F, Molassiotis A, Herrstedt J, et al; Participants of the MASCC/ESMO Consensus Conference Copenhagen 2015. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(Suppl 5):v119-v133.
24. Bower JE, Bak K, Berger A, et al; American Society of Clinical Oncology. Screening, assessment, and management of fatigue in adult survivors of cancer: an American Society of Clinical Oncology Clinical Practice Guideline Adaptation. J Clin Oncol. 2014;32:1840-1850.
25. Arends J, Bachmann P, Baracos V, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11-48.

26. Fabi A, Bhargava R, Fatigoni S, et al; ESMO Guidelines Committee. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. Ann Oncol. 2020;31:713-723.
27. Loprinzi CL, Lacchetti C, Bleeker J, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: ASCO Guideline Update. J Clin Oncol. 2020;38:3325-3348.
28. Jordan B, Margulies A, Cardoso F, et al; EANO Guideline Committee. Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO-EONS-EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up. Ann Oncol. 2020;31:1306-1319.
29. Peterson DE, Bensadoun RJ, Roila F; ESMO Guidelines Working Group. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. Ann Oncol. 2011;22(Suppl 6):vi78-vi84.
30. Elad S, Cheng KKF, Lalla RV, et al; Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO). MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2020;126:4423-4431.
31. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36:1714-1768.
32. Haanen JBAG, Carbonnel F, Robert C, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(Suppl 4):iv119-iv142.
33. Rapoport BL, Anderson R, Cooksley T, et al. MASCC 2020 recommendations for the management of immune-related adverse events of patients undergoing treatment with immune checkpoint inhibitors. Support Care Cancer. 2020;28:6107-6110.
34. Taplitz RA, Kennedy EB, Bow EJ, et al. Outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology and Infectious Diseases Society of America Clinical Practice Guideline Update. J Clin Oncol. 2018;36:1443-1453.
35. de Naurois J, Novitzky-Basso I, Gill MJ, et al; ESMO Guidelines Working Group. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21(Suppl 5):v252-v256.
36. Multinational Association of Supportive Care in Cancer. Identifying Patients at Low Risk for Febrile Neutropenia Complications. https://www.mascc.org/mascc-fn-risk-index-score. Accessed February 10, 2021.
37. Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2015;33:3199-3212.
38. Bohlius J, Bohlke K, Castelli R, et al. Management of cancer-associated anemia with erythropoiesis-stimulating agents: ASCO/ASH Clinical Practice Guideline Update. J Clin Oncol. 2019;37:1336-1351.
39. Aapro M, Beguin Y, Bokemeyer C, et al. Management of anaemia and iron deficiency in patients with cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29:iv96-iv110.
40. Benson AB, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22:2918-2926.
41. Bossi P, Antonuzzo A, Cherny NI, et al. Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2018;29:iv126-iv142.
42. Yarom N, Shapiro CL, Peterson DE, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO Clinical Practice Guideline. J Clin Oncol. 2019;37:2270-2290.
43. Coleman R, Body JJ, Aapro M, et al; ESMO Guidelines Working Group. Bone health in cancer patients: ESMO Clinical Practice Guidelines. Ann Oncol. 2014;25(Suppl 3):iii124-iii137.
44. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018;36:2326-2347.
45. Berger AM, Mooney K, Aranha O, et al. NCCN Guidelines version 1.2021, cancer-related fatigue. https://www.nccn.org/professionals/physician_gls/pdf/fatigue.pdf. Accessed March 4, 2021.
46. Ryan JL, Carroll JK, Ryan EP, et al. Mechanisms of cancer-related fatigue. Oncologist. 2007;12(Suppl 1):22-34.
47. Cederholm T, Jensen GL, Correia MITD, et al; GLIM Working Group. GLIM criteria for the diagnosis of malnutrition: a consensus report from the global clinical nutrition community. Clin Nutr. 2019;38:1-9.
48. Jensen GL, Mirtallo J, Compher C, et al; International Consensus Guideline Committee. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. JPEN J Parenter Enteral Nutr. 2010;34:156-159.
49. Arends J. Struggling with nutrition in patients with advanced cancer: nutrition and nourishment—focusing on metabolism and supportive care. Ann Oncol. 2018;29:ii27-ii34.
50. van Bokhorst-de van der Schueren MA, Guaitoli PR, Jansma EP, et al. Nutrition screening tools: does one size fit all? A systematic review of screening tools for the hospital setting. Clin Nutr. 2014;33:39-58.
51. Wakabayashi H, Arai H, Inui A. The regulatory approval of anamorelin for treatment of cachexia in patients with non-small cell lung cancer, gastric cancer, pancreatic cancer, and colorectal cancer in Japan: facts and numbers. J Cachexia Sarcopenia Muscle. 2021;12:14-16.
52. Singh P, Yoon SS, Kuo B. Nausea: a review of pathophysiology and therapeutics. Ther Adv Gastroenterol. 2016;9:98-112.
53. Naeim A, Dy SM, Lorenz KA, et al. Evidence-based recommendations for cancer nausea and vomiting. J Clin Oncol. 2008;26:3903-3910.
54. American Cancer Society. Managing nausea and vomiting at home. https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/nausea-and-vomiting/nausea-and-vomiting.html. Accessed February 8, 2021.

55. Chan A, Hertz DL, Morales M, et al. Biological predictors of chemotherapy-induced peripheral neuropathy (CIPN): MASCC neurological complications working group overview. Supportive Care Cancer. 2019;27:3729-3737.

56. Hu S, Huang KM, Adams EJ, et al. Recent developments of novel pharmacologic therapeutics for prevention of chemotherapy-induced peripheral neuropathy. Clin Cancer Res. 2019;25:6295-6301.

57. St. Germain DC, O'Mara AM, Robinson JL, et al. Chemotherapy-induced peripheral neuropathy: Identifying the research gaps and associated changes to clinical trial design. Cancer. 2020;126:4602-4613.

58. Lu W, Giobbie-Hurder A, Freedman RA, et al. Acupuncture for chemotherapy-induced peripheral neuropathy in breast cancer survivors: a randomized controlled pilot trial. Oncologist. 2020;25:310-318.

59. Greenlee H, Crew KD, Capodice J, et al. Randomized sham-controlled pilot trial of weekly electro-acupuncture for the prevention of taxane-induced peripheral neuropathy in women with early stage breast cancer. Breast Cancer Res Treat. 2016;156:453-464.

60. Tsuyuki S, Senda N, Kanng Y, et al. Evaluation of the effect of compression therapy using surgical gloves on nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: a phase II multicenter study by the Kamigata Breast Cancer Study Group. Breast Cancer Res Treat. 2016;160:61-67.

61. Tsuyuki S, Yamagami K, Yoshibayashi H, et al. Effectiveness and safety of surgical glove compression therapy as a prophylactic method against nanoparticle albumin-bound-paclitaxel-induced peripheral neuropathy. Breast. 2019;47:22-27.

62. Kanbayashi Y, Sakaguchi K, Ishikawa T, et al. Comparison of the efficacy of cryotherapy and compression therapy for preventing nanoparticle albumin-bound paclitaxel-induced peripheral neuropathy: A prospective self-controlled trial. Breast. 2020;49:219-224.

63. Loprinzi CL, Lustberg MB, Hershman DL, et al. Chemotherapy-induced peripheral neuropathy: ice, compression, both, or neither? Ann Oncol. 2020;31:P5-P6.

64. Pachman DR, Weisbrod BL, Seisler DK, et al. Pilot evaluation of Scrambler therapy for the treatment of chemotherapy-induced peripheral neuropathy. Support Care Cancer. 2015;23:943-951.

65. Loprinzi C, Le-Rademacher JG, Majithia N, et al. Scrambler therapy for chemotherapy neuropathy: a randomized phase II pilot trial. Support Care Cancer. 2020; 28:1183-1197.

66. Kanzawa-Lee GA, Larson JL, Resnicow K, et al. Exercise effects on chemotherapy-induced peripheral neuropathy: a comprehensive integrative review. Cancer Nursing. 2019;43:E172-E185.

67. Kleckner IR, Kamen C, Gewandter JS, et al. Effects of exercise during chemotherapy on chemotherapy-induced peripheral neuropathy: a multicenter, randomized controlled trial. Support Care Cancer. 2018;26:1019-1028.

68. Streckmann F, Zopf EM, Lehmann HC, et al. Exercise intervention studies in patients with peripheral neuropathy: a systematic review. Sports Med (Auckland, NZ). 2014;44:1289-1304.

69. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: Results of the PACES randomized clinical trial. J Clin Oncol. 2015; 33:1918-1927.