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Complementary and Integrative Medicine in Hematologic Malignancies: Questions and Challenges

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Abstract Hematologic malignancies represent 9.7% of all cancers, making them the fourth most common type of cancer in the United States. The aggressive and complex treatments administered in hematologic malignancies result in a high burden of psychological needs. Complementary and integrative medicine (CIM) is becoming one of the options that patients use to address their distress during and after cancer treatments. It is not clear whether appropriate CIM can relieve distress in patients affected by these malignancies. This review covers the potential benefits of CIM as relates to nutrition, nutritional supplements, exercise, circadian rhythm, methods for reducing distress during bone marrow aspiration, massage therapy, and acupuncture, in treating patients with hematological malignancies. This review may provide a framework to enhance patient-doctor dialogue regarding CIM use in hematologic malignancies.

Keywords Complementary medicine · Alternative medicine · Cancer care · Hematologic malignancies · Nutrition · Nutritional supplements · Acupuncture

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Introduction

Hematologic malignancies include leukemia, lymphoma, and myeloma and represent 9.7% of all cancers, making hematologic malignancies the fourth most common type of cancer in the United States (US) [1, 2].

These malignancies are typically treated with chemotherapy, targeted therapies, and hematopoietic cell transplantation. Advances in treatments and supportive care have increased survival rates. In the US, the 5-year survival rates range from 26.6% for acute myeloid leukemia to 86.6% for Hodgkin lymphoma [1, 2].

Treatments for hematologic malignancies are aggressive and complex and at times require long periods of hospitalization and barrier nursing to prevent infections. Treatment can result in debilitating physical and psychological side effects, including anxiety, depression, fatigue, neuropathy, nausea, vomiting, painful mouth ulcerations, and diarrhea [3–6]. Over 50% of adult patients with a hematologic malignancy report at least one unmet need in the sphere of supportive care [7], and 25% report seven or more [8]. The most common unmet needs are psychological, including anxiety, depression, fear of cancer recurrence, and cognitive problems [7–9]. Unmet needs remain high even after the completion of active treatment. Close to one third of hematological cancer survivors report unmet needs related to financial issues, emotional support, and lack of accessible information [10, 11].

Complementary and integrative medicine (CIM) is one of the options that patients with cancer use to address their distress during and after cancer treatments [12]. Worldwide, an estimated 33–47% of individuals diagnosed with cancer use complementary, alternative, or integrative therapies during cancer treatment [12].

Despite the widespread use of CIM by patients with cancer, few studies have been published about CIM use by patients

with hematological malignancies. These reports estimate that16–70% of patients with hematologic malignancies use CIM [13–17].

In one recent report of non-Hodgkin lymphoma (NHL) survivors, 89% reported using CIM: 78% took vitamins, 54% used alternative therapies, and 45% used herbal remedies [18••].

By using CIM, patients take a more active role in their treatment by trying to reduce the risk of recurrence and manage the chronic side effects of traditional cancer treatments, trying to gain control over their lives, and trying to improve their quality of life [19, 20].

Even though most patients indicate that they would prefer to get a physician's referral to use CIM, they actually do not consult this use with their physician [21••].

Most patients with cancer who use CIM view it as complementary and not as an alternative treatment [21••]. Patients believe that their physicians have limited knowledge of CIM and are not interested in discussing the benefits or problems of CIM. Many patients believe that the emphasis on scientific studies and evidence-based medicine is an obstacle to patient-doctor communication, as patients would like to discuss their individual preferences [21••].

Patients seek a reliable professional source of information and prefer to be able to engage in open communication with their doctors regarding CIM use [19, 21••]. When they feel that they cannot discuss these issues with their healthcare provider, patients may be at risk for utilizing unsafe practices that could reduce the efficacy of conventional treatments administered for curative intent.

This review will cover the benefits of CIM, including nutrition, nutritional supplements, exercise, sleep and circadian rhythm, methods for reducing anxiety during bone marrow aspiration, massage therapy, and acupuncture in patients with hematological malignancies. Nutrition support, rehabilitation therapy and psychosocial support that is recommended for patients undergoing hematopoietic cell transplantation is out of scope for the purpose of this review.

Nutrition/Diet

The World Cancer Research Fund (WCRF) and the American Institute for Cancer Research (AICR) report that 30–40% of cancers can be prevented with proper nutrition, regular exercise, and reduced rates of obesity [22].

In the "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective Expert Report," the WCRF and AICR recommend consuming a greater variety of vegetables, fruits, whole grains, and legumes; planning plant-based meals (two thirds vegetables, fruits, whole grains, or beans and one third (or less) animal protein); avoiding sugary drinks; and limiting consumption of processed foods high in added sugar, low in fiber, or high in fat [22].

In hematological malignancies, the role of nutrition is less clear than in solid tumors. In a prospective study, researchers examined the potential association between nutrition and risk of leukemia among participants in the European Prospective Investigation into Cancer and Nutrition study. Among the 477,325 participants with mean follow-up of 11.34 years, 773 participants were diagnosed with leukemia. The study did not find any significant associations between nutrition and leukemia diagnosis [23]. However, other studies have shown the benefit of nutrition for these patients [22].

Additionally, a cohort study of 568 patients with NHL, diagnosed from 1996 to 2000 with a median follow-up of 7.7 years, showed that a high intake of vegetables before diagnosis was associated with better overall survival among patients with NHL who survived longer than 6 months. The researchers concluded that increasing vegetable and citrus fruit consumption could be a useful strategy to improve survival in NHL patients [24].

Fruits and vegetables contain many potentially protective substances, including several antioxidants as well as phytochemicals with antiproliferative capabilities [22], but the safety of fresh fruits and vegetables has become an issue of concern, especially for patients with hematologic malignancies during periods of severe neutropenia when patients may be susceptible to infection related to bacteria present on fresh fruits and vegetables. The so-called "neutropenic diet" prescribes the ingestion of cooked food and avoidance of fresh fruits and vegetables to reduce and prevent infections. However, clinical trials have not shown evidence supporting the benefit of a neutropenic diet [25, 26••].

In a study at The University of Texas MD Anderson Cancer Center, 153 patients receiving induction chemotherapy for newly diagnosed acute myeloid leukemia (AML) were randomly assigned to a diet containing no raw fruits or vegetables (N = 78 cooked diet) or to a diet containing fresh fruit and fresh vegetables (N = 75 raw diet). The time to major infection and survival time were similar in the two groups. Fever of unknown origin occurred in 51% of the patients in the cooked diet group and in 36% of the patients in the raw diet group. The authors concluded that the neutropenic diet did not prevent major infection or death [25].

Another study that evaluated infectious complications during intensive treatment in 339 children with AML, found that there was no significant benefit of any of the restrictions regarding food, social contacts, and pets on the occurrence of fever, bacteremia, pneumonia, and gastroenteritis. The authors concluded that owing to the lack of effectiveness of dietary restrictions, anti-infection policies should be reconsidered [26••].

The AICR reports that certain fruits and vegetables may be beneficial in preventing cancer recurrence [27]. These foods include beans, berries, cruciferous vegetables, flaxseed, garlic,

green tea, tomatoes, and others. The AICR emphasizes that there is no single food or food constituent that can protect against cancer by itself, but the combination of foods in a plant-based diet may offer some protection [27]. In vitro studies of hematologic malignancies suggest that lemons [28], carrots [29], pomegranate [30–32], garlic [33, 34], and chocolate [35, 36] might have a role in prevention and treatment and influence future work (Table 1).

Several studies investigated whether the consumption of foods of animal origin affects the risk of developing hematologic malignancies, with conflicting results. Most of the studies mentioned in the AICR/WCRF document reported statistically significant associations between increased meat, red meat, milk and dairy consumption with increased incidence of lymphoid and hematopoietic cancers [22].

Following this report, two separate meta-analyses of observational studies investigated the association between nutrition and the risk of non-Hodgkin lymphoma found that consumption of red and processed meat may be related to increased NHL risk [37, 38]. One of the studies included 16,525 patients with non-Hodgkin lymphoma and 3665 patients with multiple myeloma from 33 independent studies. The researchers found that foods of animal origin could have a role in the etiology of non-Hodgkin lymphoma and multiple myeloma: red meat and dairy tended to increase the risk for these cancers, and fish decreased risk. The researchers concluded that their findings support the recommendations to reduce consumption of red meat and eat a diet rich in vegetables, legumes, and fish [38].

A population-based case-control study of patients with Hodgkin lymphoma had similar findings. Researchers observed increased risk of Hodgkin lymphoma with high meat intake and a diet high in desserts and sweets [39].

Many people try to reduce their sugar intake with sugar substitutes, such as aspartame, which may increase risk of hematologic malignancies. A long-term epidemiologic study with a 22-year follow-up showed that consumption of regular sugar-sweetened soda was associated with increased risk of NHL and multiple myeloma in men but not in women. On the other hand, the use of the alternative, diet soda and increased aspartame intake, increased the risk of NHL and multiple myeloma in men and leukemia in both men and women [40, 41].

Bioactive Dietary Components

Several studies have reported that green tea ingredients, mostly epigallocatechin-3-gallate, exert antitumor effects in hematologic malignancies by inducing apoptosis and suppressing angiogenesis [42–45]. However, there are few epidemiologic studies on the effects of green tea on hematological

Table 1 Hematologic malignancies—foods and supplements with possible benefit

Leukemia	Lymphoma	Myeloma
• Plant-based diet	• Plant-based diet	• Plant-based diet
• Reduce sugar, sodas, and sweets	• Reduce sugar, sodas, and sweets	• Reduce sugar, sodas, and sweets
	• High intake of vegetables	
	• Avoid milk and dairy	• Reduce red meat
		• Reduce processed meat
	• Reduce red meat	
	• Reduce processed meat	
• Citrus fruits	• Garlic	
• Carrots		
• Pomegranates		
• Green Tea	• Green Tea	• Green tea (Avoid with Bortezomib)
• Curcumin	• Curcumin	• Curcumin
• Black cumin	• Chocolate	
Supplements	Supplements	Supplements
MCP	Probiotics	MCP
Probiotics	Ashwagandha	Probiotics
Ashwagandha	Omega-3	Omega-3
Omega-3		

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MCP modified citrus pectin

malignancies; some case-control studies have suggested that green tea intake was associated with a lower risk of leukemia [46, 47]. Another study suggested that higher intake of tea flavonoids was inversely associated with the risk of non-Hodgkin lymphoma [48]. In a population-based cohort study of over 40,000 Japanese adults (9 years of follow-up), researchers documented 157 hematologic malignancies, including 119 cases of lymphoid neoplasms and 36 cases of myeloid neoplasms. The risk of hematologic malignancies was found to be inversely associated with green tea consumption [49].

In an in vitro study of the effect of green tea on multiple myeloma cell lines, researchers found that green tea ingredients prevented tumor cell death induced by bortezomib. Owing to the concern that green tea polyphenols may have the potential to negate the therapeutic efficacy of bortezomib, researchers suggested that consumption of green tea products should be avoided during cancer therapy with bortezomib [50].

By contrast to green tea, the addition of curcumin to bortezomib-induced apoptosis in leukemia cells and had additive effects with bortezomib in cellular and xenograft models [51].

Curcumin, a natural component of the rhizome of *Curcuma longa*, has been shown to have powerful chemopreventive and anticancer properties. Curcumin has been reported to exert anti-inflammatory, antiangiogenic, and antiproliferative activity in various types of cancer, including leukemia [52, 53]. Research with patients with early hematologic malignancies, including monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, or stage 0/1 CLL, suggest that curcumin may lead to prolonged survival and delay in progressive disease in some of these patients [54].

In a small study with 30 patients with relapsed or transformed follicular NHL, patients who received chemotherapy, curcumin, and green tea experienced synergistic antitumor activity and downregulated expression of all NF-κB–regulated gene products, leading to the suppression of angiogenesis and metastasis. Of the patients, 18 had a complete response, and 12 had partial response, these patients remained disease-free for a mean of 8.6 years (range, 7.9–9.2 years) after receiving this combination therapy [55].

Black cumin seeds, a commonly used spice in India and the Middle East was found to have strong antioxidant properties. The main component of black cumin is thymoquinone, which has been reported to exhibit antioxidant and anti-inflammatory effects. Black cumin has been shown to suppress the proliferation of various tumor cells, including myeloblastic leukemia [54]**.** The anticancer and anti-inflammatory activities may be mediated in part through the suppression of the NF-κB pathway [56].

A small Egyptian study of 40 children with acute lymphoblastic leukemia evaluated the effect of black cumin seeds. In this study, 20 patients received methotrexate and black cumin seeds for 1 week after each methotrexate dose and 20 patients received methotrexate and placebo. The children in the black cumin seed group had significantly less drug-induced liver toxicity and improved prognosis regarding remission and relapse [57].

Nutritional Supplements

Several studies have confirmed that a large percentage of patients with cancer use self-selected forms of complementary therapies, including nutritional supplements [58]. Many cancer patients seek advice about the proper use of nutritional supplements [59••]; unfortunately, few scientific studies have been conducted to support the use of nutritional supplements in cancer care. The WCRF and AICR recommend that nutritional supplements should be consumed only if a nutrient deficiency is either biochemically or clinically demonstrated [22].

Physicians try to base their recommendations on reliable scientific evidence, but they should not overlook the patient perspective regarding nutritional supplements. Many patients see nutritional supplements as a mean of self-empowerment which may increase quality of life [59••]. Patients have the expectation that their physician will study the appropriate use of supplements that can be helpful to their illness. If physicians ignore this element of patient care, patients are liable to seek information from less reliable sources [59••]. By discussing supplements, physicians can help guide patients away from using supplements that might carry a high risk and are likely to enhance overall patient-physician communication and improve patient satisfaction [59••].

Some examples of supplements that have been under scientific investigation are discussed below.

Modified Citrus Pectin

Modified citrus pectin (MCP), a complex polysaccharide fiber derived from the pith of citrus fruit peels blocks galectin-3. Galectins are a family of lectin molecules that affect inflammation and progression of several types of tumors including chronic myelogenous leukemia and multiple myeloma. MCP binds to galectin-3, blocks aggregation of cancer cells and prevents interaction with endothelium necessary for angiogenesis. In an in vitro study, MCP was found to have immunostimulatory properties in human blood including the activation of functional natural killer cells against K562 leukemic cells [60, 61]. MCP has minimal self-limited side effects when patients use the suggested dosage (5 g, three times a day). At times it can cause mild abdominal cramps and diarrhea, which resolves after stopping the MCP [62].

Probiotics

Probiotics are non-pathogenic live microorganisms that may have health benefits based on their immune-modulating properties. In cancer care, the main use of probiotics has been in treating intestinal toxicity during chemotherapy and radiation [59••]. Recent studies suggest that probiotics might also play a role in immunotherapy. In one study, oral administration of *Bifidobacterium* improved tumor control to the same degree as programmed death-ligand 1 antibody (immune checkpoint blockade) therapy. Interestingly, the combination of probiotics with the programmed death-ligand 1 antibody therapy almost completely suppressed tumor growth. The authors concluded that manipulating the microbiota may modulate cancer immunotherapy [63••].

Furthermore, probiotic bacteria can modulate systemic inflammation, cell proliferation, and apoptosis. A study that evaluated the molecular mechanisms of pro-apoptotic effects of human-derived *Lactobacillus reuteri* showed that L. reuteri secretes factors that potentiate apoptosis in myeloid leukemia-derived cells induced by tumor necrosis factor (TNF). This probiotic bacteria down-regulated NF-κB–dependent gene products that mediate cell proliferation (Cox-2 and cyclin D1) and cell survival (Bcl-2 and Bcl-xL). Additionally, *L. reuteri* suppressed TNF-induced NF-κB activation [64].

The main concern in probiotic use relates to safety. Infectious complications may result from bacterial translocation; one case report suggested bacteremia as an adverse event of fecal microbiota transplantation in a patient with Crohn's disease [65]. However, the use of probiotics differs from fecal transplantation. In a mouse model study, *Lactobacillus rhamnosus* GG was administered before and after hematopoietic cell transplantation. Mice that received *L. rhamnosus* had reduced graft-versus-host disease and improved survival compared with mice that did not receive the probiotic [66]. In vivo studies with rats have suggested that probiotics may actually prevent induced bacterial translocation and intestinal barrier dysfunction and, thereby, exert beneficial effects in the intestinal tract [67, 68].

Further studies demonstrated that administration of some probiotic bacteria species such as Lactobacillus to a naıve host undergoing chronic psychological stress, enhances mucosal defense against luminal bacteria, by preventing bacterial adherence to the epithelial cell surface and eliminating bacterial translocation [69].

A clinical study that evaluated the safety of probiotics in children and adolescents undergoing allogeneic hematopoietic cell transplantation found no adverse events related to the probiotics. The researchers concluded that their study provides preliminary evidence that administration of probiotics is safe and feasible in children and adolescents undergoing hematopoietic cell transplantation [70••].

Ashwagandha

Ashwagandha (*Withania somnifera*) is a popular herb in India as well as in the Middle East. Studies have suggested that this herb might be beneficial in reducing stress and anxiety in cancer patients [71] as well as in alleviating chemotherapy-induced fatigue and improving quality of life [72].

In addition to the clinical effects of this herb on quality of life, it may have some in vitro anticancer activity without affecting normal cells [73]. An in vitro study showed that ashwagandha suppressed the survival of human and murine B cell lymphoma cell lines. Furthermore, in vivo studies with syngeneic-graft lymphoma cells showed that ashwagandha inhibits the growth of tumor cells but does not affect other tissues [74]. Ashwagandha has been demonstrated to inhibit the efficiency of NF-κB nuclear translocation in diffuse large B-cell lymphomas and to significantly decrease protein levels involved in B-cell receptor signaling and cell cycle regulation [74]. Another in vitro study demonstrated that ashwagandha induces apoptosis in human T-leukemic cells and ashwagandha blocks cell proliferation through an accumulation of cells in the G2/M phase [75].

Omega-3 Fatty Acids

Omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and are principally found in fish. Humans manufacture only limited amounts of EPA and DHA from alpha-linolenic acid an essential fatty acid found in flaxseed oil, soy oil, and walnut oil. Several lines of research suggest that long-chain omega-3 polyunsaturated fatty acids have anti-inflammatory properties [76–80].

A cohort study of 70,495 residents of Washington state revealed that higher combined intake of EPA and DHA from diet and supplements was associated with a decreased risk of total mortality and mortality from cancer (HR, 0.77 [95% CI: 0.64–0.92]) [76].

In a large study involving 633 cancer survivors participating in the health, eating, activity, and lifestyle study, researchers linked higher intake of omega-3 polyunsaturated fatty acids to decreased inflammation and decreased physical fatigue, one of the main symptoms that affects cancer patients [77]. Other studies suggest that omega-3 fatty acids might also have antitumor effect. A review of the effect of omega-3 fatty acids on hematologic malignancies identified six studies: four were in vitro experiments and two used animal models. The in vitro studies found that neoplastic cells incubated with certain omega-3 fatty acids, in isolation or in combination, showed higher apoptosis induction rates [78].

In one study, omega-3 fatty acid supplements were administered to dogs undergoing chemotherapy for lymphoblastic lymphoma. Researchers observed that omega-3 fatty acids were associated with increased overall survival and disease-

free survival as compared to dogs which did not get this supplementation [79]. In another study, mice with lymphoma received diets enriched with fish oil (omega-3 fatty acids) or corn (omega-6 fatty acids) over 12 months; the fish oil diet was significantly more effective than the corn oil diet in delaying the progression of lymphoma during the first 8 months of administration [80].

In a clinical study of 16 patients who underwent bone marrow transplantation, 7 patients received 1.8 g/day of eicosapentaenoic acid (EPA) orally from 3 weeks before to about 180 days after transplantation, while 9 patients did not. All seven patients receiving EPA survived and only two had grade III graft-versus-host disease (GVHD). Among the nine patients not receiving EPA, five patients died and three had grade III or IV GVHD. In addition, thrombotic microangiopathy developed in four patients and cytomegalovirus disease occurred in four. The levels of leukotriene B(4), thromboxane A(2), and prostaglandin I(2) were significantly lower in patients receiving EPA than in those not receiving it (all $P < 0.01$). Cytokines such as tumor necrosis factor-alpha, interferon-gamma, and interleukin-10 were also significantly decreased by EPA ($P < 0.05$). The researchers concluded that patients that took EPA supplements had fewer complications and a significantly higher survival rate than patients who did not receive EPA supplements [81]. In a more recent randomized placebo-controlled clinical trial involving 70 patients with acute lymphoblastic leukemia (ALL) who were in the maintenance phase, researchers evaluated the effect of ω-3 on methotrexate hepatotoxicity. The participants were divided into a group that received oral methotrexate and ω-3 fatty acids (1000 mg/d) and a group that received methotrexate and placebo. Both groups were followed up for 6 months with frequent assessment of liver enzymes. After 6 months, liver enzymes increased in the placebo group. On the other hand, the addition of ω-3 to methotrexate maintained normal liver function and oxidant-antioxidant levels among this group of patients. No adverse reactions due to ω-3 supplementation were reported. The researchers concluded that on the base of their study, ω-3 fatty acids ameliorated methotrexate -induced hepatotoxicity and could be safely used during the maintenance phase of ALL [82••].

Exercise

Physical activity during treatment of various cancers, including hematologic malignancies, improves cardiovascular and muscular fitness and positively affects various emotional and physical outcomes such as fatigue, anxiety, depression, self-esteem, mood, and general quality of life [83–86].

Recent research has shown that increased insulin-like growth factor receptor levels are a potential driver of hematologic malignancy development [87]. Several reviews and meta-analyses have demonstrated that physical activity interventions are effective at reducing insulin-like growth factor-I in cancer survivors after treatment and could slow the disease process [88–91].

Specifically in patients with lymphoma, physical activity has been shown to be feasible and efficacious for improving sleep-related outcomes, physical function, fatigue, happiness, depression scores, cardiovascular fitness, balance, body composition, and overall quality of life [92–96]. Furthermore, exercise interventions did not interfere with chemotherapy completion or treatment response [94, 95]. In patients with leukemia, exercise interventions demonstrated significant improvements in cardiovascular fitness, functional fitness, and reduction of anxiety [83, 96].

Even though there is a need for more research to document the benefit of exercise in hematologic malignancies, there is enough evidence to motivate patients to participate in some form of physical activity to improve their quality of life and possibly affect disease progression.

Circadian Rhythm

During the awake and sleep cycles of circadian rhythm, serum melatonin levels vary with daylight exposure. Circadian rhythm disruption, such as night shift work, has been suggested as a possible contributor to the development of some hematologic malignancies [97–100]. One study showed that serum melatonin levels were considerably lower in patients with chronic lymphocytic leukemia than in healthy individuals, and these patients' prognoses were related to changes in circadian molecular signaling [101].

Melatonin, which is produced by the pineal gland mostly during the night, regulates diverse processes including immune function which may have effects on several types of cancer. Melatonin exerts strong antitumor activity via several mechanisms, including antiproliferative and pro-apoptotic effects and potent antioxidant activity on solid tumors as well as hematologic malignancies [102].

Epidemiological studies suggest that increased sun exposure may be associated with a decreased risk of developing non-Hodgkin lymphoma [103–106]. An efficacy trial showed that chemotherapy-related fatigue among cancer survivors was significantly reduced among those who were exposed to morning bright light [107]. Morning bright light treatment may also prevent overall fatigue from worsening during chemotherapy [108].

With the available data, it seems safe to suggest to patients to have some exposure to early morning sun and to sleep in dark rooms to prevent circadian rhythm disruption and promote melatonin production.

CIM for Reducing Distress During Bone Marrow Aspiration

Bone marrow aspiration is an invasive procedure frequently performed in patients undergoing evaluation for hematologic malignancy. Local anesthesia is the standard treatment to reduce pain during this procedure. Local anesthesia reduces the sharp pain of the bone marrow needle piercing the skin and periosteum but does not control pain during the suction of bone marrow. Between 40 and 64%, patients report moderate to severe pain during this procedure [109].

Any procedure that causes pain may generate significant fear and anxiety, which can affect quality of life, and reduce adherence to prescribed medications and treatments. As a result, some patients seek CIM alternatives to reduce distress and anxiety [110].

One study of patients undergoing bone marrow aspiration and biopsy suggested that viewing a nature scene during the procedure and listening to relaxing sounds may reduce pain [111]. In a study of a similar procedure, excisional breast biopsy and lumpectomy, which causes similar distress, a 15-min presurgical self-hypnosis session decreased multiple symptoms, including nausea, pain, and fatigue. Patients who underwent self-hypnosis spent less time in the operating room and the recovery room and needed less anesthesia than the control group. As a result, self-hypnosis made the procedure more cost-effective, saving the hospital nearly US$800 per patient [112].

Another modality is magnetic acupressure. In a controlled trial, cancer patients without previous acupuncture or acupressure experience were randomized to having magnetic acupressure delivered to either the large intestine 4 (LI4) acupoint or a sham site. The acupressure was well tolerated and appeared to reduce the proportion of patients with severe pain associated with bone marrow aspiration [113].

In one study of children with cancer, massage therapy was used to reduce pain and anxiety during bone marrow aspiration. The children used visual analogue scales to report their pain and anxiety levels which were significantly reduced in the massage therapy group [114].

Massage Therapy

Bone marrow transplant is a procedure that is commonly used in hematologic malignancies and is physically and emotionally demanding, frequently causes distress, anxiety, and depression. Nurturing touch is a fundamental human need that is not always met in this process. Massage therapy promotes wellbeing and provides comfort for patients who undergo bone marrow transplant. As a result, some bone marrow transplant units include massage therapy to their care [115, 116].

There are few studies about the effects of massage therapy on patients undergoing bone marrow transplant. One study showed that massage significantly improved quality of life. Patients felt less depressed and anxious, were more relaxed, had improved quality of sleep, and experienced increased alertness when they were awake [60]. In another small study of children who underwent bone marrow transplant, massage therapy resulted in decreased overall symptom burden, fewer days of mucositis, fewer reports of feeling tired and run-down, and fewer reports of pain, nausea, depression, and fatigue [117].

Patients with hematologic malignancies often go through periods in which human touch is limited owing to isolation and fear of infections. Many patients who undergo high-dose chemotherapy need to have limited social interactions. This lack of touch and reduced human contact can be an especially difficult and stressful experience. Massage therapy is often used to address these patients' need for increased human contact [118].

In a meta-analysis on the effects of massage therapy in patients affected by cancer, researchers found that massage therapy significantly reduced cancer pain compared with no massage treatment or conventional care. Among the various types of massage, foot reflexology was the most effective [119].

Several studies have suggested that massage therapy may alleviate a wide range of symptoms, including pain, nausea, anxiety, depression, anger, distress, and fatigue in patients with cancer [120–122].

One study of patients with acute myeloid leukemia revealed that patients who received massage had significant improvements in levels of stress and health-related quality of life compared with patients who did not receive massage [123].

Acupuncture

One of the common side effects of antineoplastic chemotherapy is bone marrow suppression, including thrombocytopenia, leukopenia, and lymphopenia. Clinical trials and preliminary animal studies indicate that acupuncture therapy during chemotherapy may alleviate myelosuppression via a potential myeloprotective effect [124–128]. Acupuncture is relatively inexpensive, has few side effects, and can also improve emotional state and quality of life. Further research is required in order to determine the optimal strategy for incorporating it into myelosuppressive chemotherapy regimens [124–128]. Several studies have also suggested the benefit of acupuncture in treating chemotherapy-induced peripheral neuropathy [129–132] for which there is currently no effective treatment, to prevent or treat.

Bortezomib-induced peripheral neuropathy is one of the most common toxicities in the treatment of multiple myeloma and affects 37–44% of patients; at times, bortezomib-induced peripheral neuropathy is severe enough to require dose reduction or early termination of this effective treatment [133]. Researchers from the University of Maryland Marlene and Stewart Greenebaum Cancer Center and The University of Texas MD Anderson Cancer Center studied the value of acupuncture in addressing bortezomib-induced peripheral neuropathy in separate studies. Both groups of researchers came to similar conclusions: acupuncture appears to be safe and feasible and produces subjective improvements in patients' symptoms [134, 135, 136••, 137].

Conclusion

Patients with hematologic malignancies have a high burden of unmet physical and psychological needs. CIM is an option that patients and their families use to address their distress during and after cancer treatments. Increasing scientific evidence supports the use of CIM in a supervised setting. Healthcare team members should be aware of CIM options and consider discussing CIM with their patients and patients' families. CIM has the potential to reduce the distress that these patients experience in certain situations. Additional further research in this field is needed, to expand knowledge towards improved patient care in patients suffering from hematologic malignancies.

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Compliance with Ethical Standards

Conflict of Interest Moshe Frenkel and Kenneth Sapire declare they have no conflict of interest.

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