



Integrative Approaches in the Treatment of Patients Affected by Lymphoma

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Abstract

Purpose of Review Lymphoma is the most frequent hematological malignancy with wide disease spectrum of watchful waiting period, active treatment, survivorship, and palliative care. All these steps impose unmet needs in terms of prevention, symptom alleviation, or prognosis. Complementary and integrative medicine (CIM) is widely used by patients with lymphoma to cope with such issues. Here, we describe the different CIM modalities that may be effective and safe for the management of patients with lymphoma.

Recent Findings Low inflammatory diet and ginseng seem effective for lymphoma prevention. Pain and neuropathy may be improved using acupuncture, touch therapy and specific dietary supplements. Nausea/vomiting, fatigue, and insomnia may be relieved by acupuncture, mind-body, touch therapy, and certain dietary supplements. Vitamin D, curcumin, and some traditional medicine herbs may positively impact lymphoma prognosis. Finally, safety issues should be considered especially for the concomitant use of dietary supplements and lymphoma-directed therapies.

Summary CIM may be beneficial along the continuum of lymphoma management although safety concerns should be considered when used concomitantly with conventional therapy.

Keywords Integrative medicine · Lymphoma · Complementary medicine · Haemato-oncology

Introduction

Lymphoma is the most prevalent hematological malignancy in the world [1]. Due to scientific progress with novel therapies and better supportive care in the last decades, overall survival (OS) has increased [2]. Throughout the disease course, patients may experience different physical and psychological symptoms related to both the disease and its

treatment, while conventional medicine may offer limited effectiveness [3]. This may explain why 50–70% of patients with lymphoma use complementary and integrative medicine (CIM), which is a higher rate than in the general population [4–6]. These patients reported high satisfaction from CIM, although most of them did not report such use to their hematologist [6]. Moreover, some lymphoma patients use alternative therapies to cure their disease, sometimes without informing their physicians [7], or as alternatives to conventional therapies [8]. This alternative context of care imposes significant safety-risk and ethical issues. For these reasons, a new concept of integrative hematology was coined along recent years, scientifically exploring CIM modalities in the hematology setting, which include mind-body, nutrition and supplements, touch, and acupuncture [9, 10••]. Here, we present a review of the different integrative treatments studied in lymphoma care in the context of prevention, symptomatic alleviation, impact on disease course, management of survivors, and safety issues.

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Integrative Medicine for Lymphoma Prevention

Due to the relatively high prevalence of lymphoma, attempts to prevent this disease are essential. Here, we summarized the main findings on nutrition and dietary supplements for this purpose and added recommendations in Table 1.

The association of dietary fat intake with incidence of non-Hodgkin lymphoma (NHL) has been evaluated based on two prospective studies with over 24–30 years of follow-up. While the first half of the study (1980–1994) indicated that higher fat intake was associated with increased risk of diffuse large B-cell lymphoma (DLBCL), this was not confirmed in the second half of follow-up (1994–2010) [11]. A meta-analysis of observational studies did not find strong evidence on the supposed relationship between meat intake and NHL [12].

On the other hand, the data on the increased risk of NHL with pro-inflammatory diet was confirmed in a few studies. An Italian multicenter case-control study suggests that a high dietary inflammatory index, which is a scoring algorithm that classifies individuals' diets based on their inflammatory potential, is associated with increased risk of NHL (Odds Ratio, OR 1.6), particularly in men (OR 2.1) [13]. The inflammatory score of the diet, a similar algorithm, seems to be positively associated with the risk of B-cell lymphoma (BCL) as well [14]. Specifically, an exposome-wide association study investigated the association of anthropometry (person's size, form, and functional capacities) and lifestyle factors with BCL in 475,426 subjects. The study included a principal component analysis which investigated the different exposures merged into 22 principal components, six of them were significantly associated with risk of lymphoma. Anthropometry measures, sugar and confectionary, dairy products, and physical activity among women were associated with increased risk of BCL, while fish/shellfish, vitamin D, and Mediterranean diet (with lower inflammatory state) decreased the risk of BCL [15•]. A prospective study, conducted between 1991 and 2001 in 10 European countries, suggests that adherence to Mediterranean diet seems to be associated with decreased lymphoma risk [16]. Mechanisms of action of this phenomenon are related to the anti-inflammatory and antioxidant properties of the Mediterranean foods, as well as their positive influence on insulin sensitivity, and modulation of gut microbiota composition (Fig. 1), which are associated with the incidence of cancer in general and lymphoma in particular [17].

In contrast to the above nutrition research, studies on the role of dietary supplements in lymphoma prevention are relatively limited. In a prospective cohort study on

65,732 Chinese women, ginseng consumption was associated with decreased risk of NHL (hazard ratio, HR 0.57) [18]. On the other hand, the association of vitamin D ingestion with the incidence of NHL is equivocal [19]. Finally, a systematic review and meta-analysis of cohort studies on micronutrient intake and the risk of hematological malignancies showed that vitamin A, C, D, E and lycopene did not impact the risk of NHL [20].

Symptom Relief During Active Lymphoma Treatment

Patients with lymphoma experience various physical and psychological signs during active therapy. Here, we chose to review the effect of different CIM modalities on the most experienced symptoms and summarized the recommendations in Table 1.

Pain

Pain is one of the more debilitating concerns challenging patients with lymphoma, with limited effectiveness of conventional therapies, mainly associated with adverse effects [21].

Acupuncture is listed as one of the more effective treatments of pain in patients with solid tumors [22••]. Limited research is also evident in regard to hematologic malignancies [23••]. The mechanism of action seems to be via nervous and immune system modulation including neuromodulator and neurotransmitter production as well as decreased secretion of pro-inflammatory cytokines (Fig. 1) [23••].

Another field of CIM practice that may alleviate pain include manual therapies, such as therapeutic touch, which seems to improve pain sensation and biochemical parameters in patients with cancer [24]. Specifically, the effect of foot reflexology applied along five consecutive days was studied in a randomized controlled trial (RCT) conducted in Iran in 72 patients diagnosed with lymphoma, while being compared to standard-of-care (SOC). The researchers reported a significant reduction in the degree of pain in the reflexology arm [25]. Another RCT conducted in southeastern USA with 86 cancer patients, 8 of them with lymphoma, investigated the effect of reflexology administered by patients' partner after being taught by a nurse reflexologist as compared to SOC [26]. After the initial partner-delivered foot reflexology, a patient's pain significantly decreased [26]. The proposed mechanism of the analgesic effect of touch therapy in cancer and lymphoma is the induction of local biochemical changes in the soft tissues which improves oxygenation and blood flow, as well as endorphin and vasopressin secretion (Fig. 1), allowing pain relief [27].

Table 1 Recommendations for the use of complementary and integrative modalities for lymphoma prevention and management

Indication	CIM modality	Effectiveness	Regimen
Lymphoma prevention	Nutrition		
	Fat intake [11]	Not confirmed	Not assessed
	Meat intake [12]	Not confirmed	
	Pro-inflammatory diet [13, 14]	Increased risk of BCL	
	Sweets [15•]		
	Dairy products [15•]		
	Fish/shellfish [15•]	Decreased risk of BCL	
	Mediterranean diet [15•, 16]		
	Dietary and herbal supplements		
	Vitamin D [19, 20]	Equivocal	Not assessed
Vitamin A, C, E, lycopene [20]	No effect	Not assessed	
Ginseng [18]	Decreased risk of NHL	Not assessed	
Symptom relief			
Pain	Acupuncture [23••]	Pain reduction, including during active treatment	Different protocols
	Therapeutic touch Foot reflexology [25]	Significant reduction in pain level vs SOC, can be delivered by caregiver	Five consecutive days
CIPN	DHS		
	Carnitine [29]	Reduced incidence of CIPN related to oxaliplatin in rats	30–100 mg/kg × 2/week for 4 weeks
	Chamomile [30]	Decrease CIPN pain and inflammation in mice	Not assessed
	Salvia officinalis [31]		Not assessed
	Glutamine [32]	Improved sensory function and QoL in children with vincristine CIPN	Up to 20 g daily
	Vitamin B complex [33]	Reduced CIPN perception vs placebo	1 capsule bid
	Therapeutic touch Foot massage [34]	Improved pain and sleep vs SOC	1/week for 4 weeks
Acupuncture [35, 36••]	Pain relief, improved QoL Better when combined with other CIM modalities	1–2/week for 6 weeks	
CINV	Acupuncture [23••, 38]	Decreased CINV severity, equivocal effect on frequency	Different protocols
	Mind-body Hypnosis [38]	CINV relief in children and young adults	Different protocols
	Therapeutic touch [24]	Reduced nausea duration in cancer patients	Different protocols
	DHS Ginger [41, 42]	Reduced CINV incidence and CINV-related QoL	0.8–1.2 g daily
CRF	Therapeutic touch Reflexology [25, 45] Chinese massage [45]	Significantly reduced CRF severity	Different protocols
	Mind-body Qigong [46]	Improved CRF severity and worse fatigue	2/week for 3 weeks
	Yoga [47]	Improved CRF severity	Home-based
	Music therapy [48]	Improved CRF severity vs SOC	1–8 sessions of 20–45 min
	Acupuncture [49]	Improved CRF in breast cancer patients	Different protocols
	Ginseng [50, 51]	Improved CRF symptoms	2 g daily

Table 1 (continued)

Indication	CIM modality	Effectiveness	Regimen
Sleep	Therapeutic touch Foot reflexology [25, 34]	Improved sleep quality	3/week for 4 weeks
	Mind-body Qigong [46]	Improved sleep quality and worse fatigue	2/week for 3 weeks
	Yoga [47, 52, 53]	Inconclusive, may lower sleep disturbance and decrease use of sleep medications	3 sessions of Tibetan yoga
Lymphoma prognosis	Nutrition Normal or mildly impaired nutritional status [55••, 56–60]	Improved ORR, CR, PFS and OS in DLBCL and TCL	CONUT score < 2–4, GNRI score
	Neutropenic diet [62•]	No impact on infection rate or mortality	Not clearly defined
	Dietary and herbal supplements Vitamin D [63•, 64–68, 69•, 70•, 71–73]	25(OH)-vitamin D < 20–30 ng/mL associated with lower OS in untreated and treated pts. Vit D3 supplement improved EFS if deficient	To replete vitamin D level
	Curcumin [74, 75]	In vitro additive effect to doxorubicin	5 μM in vitro
	EGCG [79, 80]	Potential reduction of burden of disease	2 g bid
	TCM and TKM [81–83]	Potential positive effects according to case reports	Not assessed
Survivors	Mind-body Qigong [96•]	Improved anxiety, depression, and HRV	16 sessions
	Relaxation [97]	Improved QoL, less effective than exercise	50 min, 3/week for 12 weeks
	Tibetan yoga [53]	Improved sleep quality, no effect on anxiety, fatigue, depression	3 sessions
	Nutrition Fatigue reduction diet [98•]	Improved diet quality and reduced fatigue (pilot study)	Specific fruits, vegetables, whole grains and omega-3 fatty acid-rich foods: 12 weeks

BCL B-cell lymphoma, *bid* twice daily, *CR* complete remission, *CIM* complementary and integrative medicine, *CINV* chemotherapy-induced nausea and vomiting, *CIPN* chemotherapy-induced peripheral neuropathy, *CONUT* controlling nutritional status score, *CRF* cancer-related fatigue, *DHS* dietary and herbal supplements, *DLBCL* diffuse large B-cell lymphoma, *EFS* event-free survival, *EGCG* epigallocatechin gallate, *GNRI* geriatric nutritional risk index, *HRV* heart rate variability, *min* minutes, *NHL* non-Hodgkin lymphoma, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *QoL* quality-of-life, *SOC* standard of care, *TCL* T-cell lymphoma, *TCM* Traditional Chinese Medicine, *TKM* Traditional Korean Medicine

Chemotherapy-Induced Peripheral Neuropathy (CIPN)

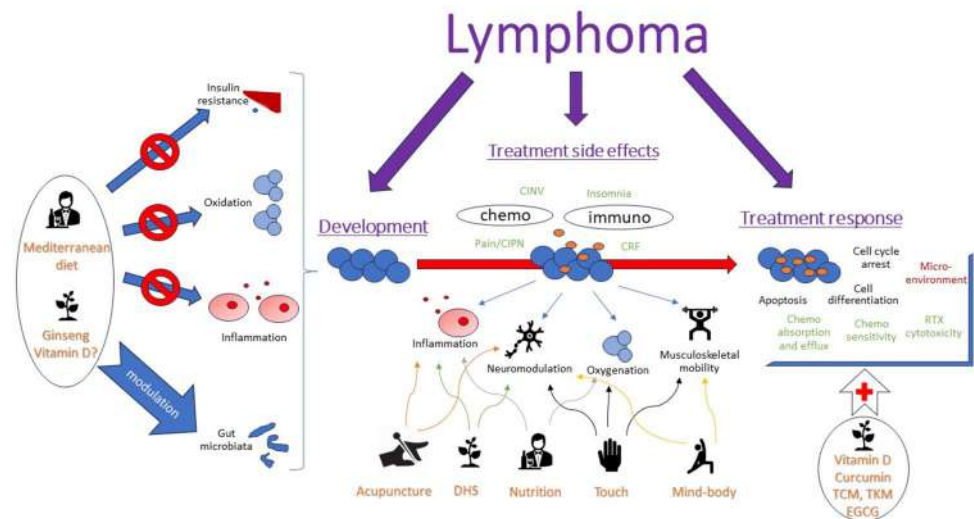
CIPN is a frequent symptom in patients with lymphoma and is associated with impaired quality-of-life (QoL). However, conventional drugs have limited effectiveness in alleviating this challenging concern [28].

In preclinical models, carnitine reduced the incidence of oxaliplatin-related CIPN, although no clinical study currently confirms this data [29]. In mouse models, *Matricaria chamomilla* and *Salvia Officinalis* hydroalcoholic extracts seemed to decrease pain and inflammation in CIPN [30, 31].

Glutamine dietary supplement has been compared to placebo in 56 children and adolescents with vincristine-related CIPN, most of them with lymphoma. While no major side effect was noted, there was a significant improvement in the sensory function and QoL in the intervention group [32]. Finally, vitamin B complex supplementation has been shown to reduce the perception of sensory vincristine and oxaliplatin-related CIPN as compared with placebo in a RCT with 71 patients, 28% of them with lymphoma, although it did not reduce its incidence [33].

Manual therapy seems to be beneficial as well for this indication. An interventional study evaluated the effect

Fig. 1 Mechanisms of action of the different integrative medicine modalities on lymphoma development, side effects, and response to treatment. Chemo: chemotherapy; CINV: chemotherapy-induced nausea and vomiting; CIPN: chemotherapy-induced peripheral neuropathy; CRF: cancer-related fatigue; DHS: dietary and herbal supplements; EGCG: epigallocatechin gallate; Immuno: immunotherapy; RTX: rituximab; TCM: Traditional Chinese Medicine; TKM: Traditional Korean Medicine.



of three 20-minute weekly sessions of foot massage for 4 weeks in NHL patients with CIPN and showed symptomatic improvement including pain and sleep as compared to the control group [34].

A recent integrative review has shown that acupuncture may decrease pain and improve QoL in cancer patients with CIPN [35]. Most of the studies reviewed included lymphoma patients, and a review that focused on hematologic malignancies showed moderate evidence for the relief of CIPN-related patients with acupuncture treatment [23••]. Finally, a recent Israeli RCT on 168 patients with CIPN, some of them with lymphoma, evaluated the effect of acupuncture alone or with other CIM modalities vs SOC. This study showed that acupuncture relieved CIPN-associated symptoms and improved QoL and that emotional well-being, physical functioning, and pain improved even more with the addition of other CIM modalities [36••].

Chemotherapy-Induced Nausea and Vomiting (CINV)

CINV is a common symptom challenging patients with solid and hematological malignancies. The mechanism involves the release of mediators such as serotonin or substance P by chemotherapy affecting the vagal afferent pathway [37]. Cyclophosphamide and doxorubicin, which are frequently prescribed in lymphoma protocols, are highly emetogenic [37].

A meta-analysis of RCTs showed that both acupuncture and hypnosis were effective for relieving CINV in children and young adults [38]. The efficacy of acupuncture on the reduction of CINV has been specifically evaluated in a few studies, some of which including patients with lymphoma [23••]. In many of these studies, acupuncture seems to

decrease the severity of CINV, although its effect on the frequency of this symptom is controversial [23••].

Although not specifically evaluated in patients with lymphoma, therapeutic touch has been shown to reduce the duration of nausea in cancer patients receiving chemotherapy [24]. Mechanisms of action of both therapeutic touch and acupuncture in the relief of CINV seem to be related to their effect on the autonomic nervous system (Fig. 1) [24, 39].

Finally, in numerous studies, ginger has been shown to have antiemetic effects, including among cancer patients in which it may reduce the incidence of acute chemotherapy-induced vomiting [40•]. In a RCT conducted among 45 patients with hematological malignancies receiving chemotherapy, a dosage of 800 mg of ginger was compared with antiemetic drugs provided to the control group. It was found that ginger significantly reduced the incidence of CINV in patients with haemato-oncological conditions [41]. Following these results, a double-blind placebo-controlled RCT investigated the effect of 1.2 g of standardized ginger on CINV-related QoL in 51 patients with cancer undergoing moderately to highly emetogenic chemotherapy, 11 of them with lymphoma [42]. This study showed that ginger may significantly improve CINV-related QoL [42]. Few mechanisms of action of this herb seem to contribute to this effect, including the interaction of several pathways implied in the pathophysiology of CINV or its exacerbation, such as antagonism to serotonin, substance P or acetylcholine receptor, anti-inflammatory properties, or modulation of cellular redox signaling (Fig. 1) [43].

Cancer-Related Fatigue

Cancer-related fatigue (CRF) is experienced by more than 80% of patients receiving chemotherapy, with a prevalence of 50% among patients treated with lymphoma [44].

A meta-analysis of RCTs has examined the effect of massage therapy in general in cancer patients and showed both reflexology and Chinese massage may significantly reduce the severity of CRF [45]. Reflexology was also specifically evaluated in 72 patients with lymphoma in an Iranian RCT reporting a significant improvement in CRF severity as compared with SOC [25]. The proposed mechanism of touch therapy is the mechanical pressure that increases muscle compliance and joint mobility and therefore improves fatigue sensation (Fig. 1) [45].

Numerous mind-body interventions have been evaluated as well for this indication. For example, a single-center RCT investigated the effect of twice daily qigong for 3 weeks as compared to SOC in 108 patients with NHL receiving chemotherapy and showed a significant improvement in average fatigue severity and in worse fatigue in the qigong group as compared to SOC [46]. A feasibility study evaluated the effect of home-based yoga in 14 patients with lymphoma undergoing chemotherapy and showed that while no adverse events were noted, it seemed that yoga improved the level of fatigue [47].

Music therapy was evaluated as well in a meta-analysis of six RCT on 279 patients with hematological malignancies including about half with lymphoma and found that 1 to 8 sessions of 20 to 45 minutes were effective in reducing the severity of CRF in this group of patients [48].

Acupuncture as well has been shown to relieve CRF, although the best effect was encountered among breast cancer patients [49].

Finally, ginseng which has been widely evaluated for the treatment of CRF, was also assessed specifically among patients with lymphoma [50, 51]. A systematic review of 5 studies has shown that 2 g daily of American ginseng improves symptoms related to CRF [51]. Side effects were rare, and no clinically significant drug interactions were noted, so that this herbal supplement can be used safely concomitantly with lymphoma treatment. Other herbal supplements have been evaluated for the relief of CRF but not specifically in lymphoma.

Sleep Quality

Insomnia and poor sleep quality are frequently reported in patients undergoing cancer therapy and may be experienced by about half of patients with lymphoma [25]. While conventional treatments are limited for this condition, CIM techniques may be helpful.

Indeed, an Iranian RCT evaluating the effect of reflexology on 72 patients with lymphoma as compared to SOC concluded an improvement of sleep quality in the intervention as compared to the control group [25]. Another study evaluating the effect of 3 weekly sessions of foot massage for 4 weeks administered to patients with NHL showed an

improvement in sleep quality following foot massage [34]. As previously noted, touch therapy may act by mechanical pressure that increases muscle compliance and joint mobility and therefore improves sleep quality (Fig. 1) [45].

Mind-body techniques have been evaluated as well for this indication. Indeed, the previously described RCT of qigong vs SOC in patients with NHL undergoing chemotherapy showed qigong improved overall sleep quality as compared to the control group [46]. While primary data on the effect of yoga on sleep in patients with NHL were inconclusive in both a feasibility study [47] and a systematic review [52], a RCT that compared the effect of at least 3 Tibetan yoga sessions with waiting list in 89 lymphoma patients demonstrated a lower sleep disturbance score in the intervention group, including all improved subjective sleep quality, faster sleep latency, longer sleep duration, and decreased use of sleep medications [53]. The proposed mechanisms of action include action of yoga on the autonomic nervous system (sympathetic downregulation, parasympathetic activation) that may improve sleep quality (Fig. 1) [54].

Effect of Integrative Medicine on the Course of Lymphoma

Although the current treatments of lymphoma are very advanced including novel therapies, some patients are still refractory to treatment or relapse after achieving remission. Therefore, integrative attempts to improve treatment and prognosis should be investigated, and the current data is summarized in Table 1.

Nutrition

An adapted nutrition is a major factor for prognosis in lymphoma. Indeed, the controlling nutritional status (CONUT) score, which is an index combining serum albumin, total cholesterol and lymphocyte counts reflecting both nutrition and inflammation, has been shown to independently affect prognosis of patients with BCL and T-cell lymphomas (TCL). In three independent retrospective analyses of patients with DLBCL, a low CONUT score (< 4) reflecting normal and mildly impaired nutritional status was associated with better progression-free survival (PFS) and OS [55••, 56, 57]. Similar data was obtained in TCL. Indeed, a case-control study in 99 patients with peripheral TCL showed that a CONUT score of 5 and higher was an independent factor for decreased survival [58], and a retrospective study of extranodal NK/TCL patients treated with asparaginase showed that a better nutritional status (CONUT score < 2) improved response rates, PFS, and OS [59]. The geriatric nutritional risk index (GNRI), a similar score including height, weight, and serum albumin and adapted to older

patients, has been shown in a retrospective analysis of patients with DLBCL to impact PFS and OS as well [60]. These data seem to be related to the negative effects of malnutrition and sarcopenia in patients treated with chemotherapy for lymphoma [61]. Therefore, an adapted diet which keeps such nutritional scores in the normal or near-normal range is essential for patients with all types of lymphoma.

On the other hand, a systematic review with meta-analysis of 6 studies including 1114 patients on the effect of a “neutropenic diet” in oncologic patients with neutropenia showed that such a diet did not significantly improve infection rate or mortality [62•]. Therefore, and although more studies are needed to confirm these findings, there is no evidence for recommending a neutropenic diet to patients with lymphoma.

Vitamin D

Vitamin D deficiency has been shown in multiple studies to be associated with poor prognosis in patients with lymphoma at pre-treatment [63•, 64], including in Hodgkin lymphoma [65], DLBCL [66], follicular lymphoma [67], and TCL [66]. An observational study has shown that baseline vitamin D deficiency was more common in obese lymphoma patients at diagnosis and did not change one month after initiating lymphoma treatment [68]. Similar data have been found in treated lymphoma patients. For example, an observational study including 111 adults with relapsed/refractory (R/R) DLBCL pre-CAR-T showed that patients with vitamin D insufficient levels ($25(\text{OH})\text{-D} \leq 30 \text{ ng/mL}$) had lower response rates, OS and viability of tisagenlecleucel than repleted patients [69•]. Similar results were observed in patients with R/R DLBCL treated with lenalidomide-rituximab-GDP protocol (R2-GDP) [70•]. Following these data, an Italian study evaluated the effects of vitamin D3 (cholecalciferol) supplementation on the prognosis of high-grade BCL patients treated with R-CHOP and found that $25(\text{OH})\text{-D} < 20 \text{ ng/mL}$ was an independent negative prognostic factor and that cholecalciferol supplementation improved event-free survival in such patients [71]. The mechanism of action of this phenomenon has been investigated, and in vitro data suggest that vitamin D supplementation may enhance rituximab-mediated cytotoxicity (Fig. 1) [72]. Indeed, vitamin D seems to promote apoptosis, induce differentiation, and inhibit proliferation of lymphoma cells, while reducing the production of pro-inflammatory cytokines and sensitizing tumor cells to anti-cancer therapy [73]. Moreover, vitamin D seems to have immunomodulatory properties according to a human study on patients with DLBCL treated with R2-GDP protocol which showed that vitamin D deficiency was associated with increased level of immune suppressor cells that were depleted in patients with normal levels of vitamin D with better response to treatment

[70•]. Finally, an in vitro and xenograft study showed that vitamin D supplementation increased chemosensitivity of Hodgkin lymphoma cells [65]. Vitamin D3 is well-tolerated in patients with lymphoma [73], and following these data, cholecalciferol supplementation should be considered in all lymphoma patients with vitamin D deficiency (Table 1).

Curcumin

Spices used in Mediterranean diet, including ginger, pepper, rosemary, turmeric (curcumin), black cumin, and clove, have been shown to have therapeutic and preventive properties in different cancers [74]. Specifically, the effects of curcumin have been demonstrated in the treatment of both Hodgkin and NHL. Indeed, in vitro and in vivo pharmacokinetic studies have shown the additive effect of curcumin ($5 \mu\text{M}$) with the chemotherapy doxorubicin (0.4 mg/mL) and the effect of this supplement on enhancing absorption and decreasing the efflux of this chemotherapeutic drug in Hodgkin lymphoma [75]. As for BCL, in vitro and in vivo studies have shown the effect of curcumin on apoptosis promotion and cell cycle arrest that are mediated by PPAR γ promotion and Akt/mTOR pathway inactivation [76]. Finally, when combined with the translation inhibitor omacetaxine in an in vitro study, curcumin seemed to act on the microenvironment of BCL by inhibiting angiogenesis via inhibition of VEGF/Akt signaling pathway [77]. For these reasons, one should consider advising the use of curcumin in patients with lymphoma after verifying the safety of this spice in each specific patient (Table 1).

Epigallocatechin Gallate (EGCG)

Green tea catechins are well studied for their anticancer effect, including the lymphoma setting. Their action includes inhibition of the cell cycle, induction of apoptosis, and autophagy, through the inhibition of the epithelial-mesenchymal transition process [78]. Among the catechins, epigallocatechin gallate (EGCG) is the most abundant in green tea and the most studied in a clinical setting. At a dosage of 2 g twice daily, it was well tolerated and associated with a reduction in lymphocytes and lymphadenopathies after 6 months of treatment in patients with early stage chronic lymphocytic leukemia according to both phase 1 and 2 studies [79, 80].

Traditional Chinese and Korean Medicine

A few case reports have shown the positive effects of Traditional Korean Medicine [81, 82] and Chinese Medicine (TCM) [83] herbal supplements for the treatment of different kinds of aggressive lymphomas in patients with no other treatment options due to age or comorbidities. These have been supported to some extent in in vitro studies [7].

Mechanisms of action have been investigated in *in vitro* and animal/xenograft studies as well as network pharmacological-based analyses. Some TCM herbs may enhance lymphoma cells' apoptosis and cell cycle arrest (Fig. 1) [84, 85], mainly by upregulating reactive oxygen species [86, 87], or activating caspases [88–90], or may act on the microenvironment by modulating toll-like receptor pathway [91]. Some studies have even indicated synergistic effects of these herbs with chemotherapy prescribed in lymphoma such as doxorubicin or cisplatin [90–92]. The most cited herbs were Qi-invigorating TCM supplements that may explain that one of the TCM syndromes of cancer is “Qi deficiency” manifested by fatigue and reduced QoL [88]. This theory has been enhanced in an animal study demonstrating that “reviving energy/Qi” by qigong treatment of mice with lymphoma reduces the growth of lymphoma cells as compared to sham control [93].

Lymphoma Survivorship and Integrative Medicine

A survey has shown that 61% of NHL survivors use CIM and that such use was associated with a higher perception of cancer-related control and more positive mental functioning [94]. A review on the use of different integrative modalities has shown that physical activity, diet, dietary supplements, mind-body, acupuncture, and touch therapies may improve both physical and emotional issues in cancer survivors in general [95].

With lymphoma survivors, mind-body techniques are most investigated. Indeed, a RCT comparing the effect of 16 sessions of qigong with SOC among NHL survivors indicated a significant improvement in anxiety and depression levels notable also in heart rate variability with large effect sizes [96•]. Relaxation on the other hand has been shown to be less effective than exercise for the improvement of QoL in a RCT of 46 lymphoma survivors, although both techniques showed significant improvement as compared to baseline [97]. As previously described, Tibetan yoga has been evaluated in patients with lymphoma, some of them survivors, in a RCT on 89 patients and showed improvement in sleep quality in this population, with no effect on psychological outcomes [53].

In the field of nutrition, a pilot study evaluated the feasibility of a 12-week remote fatigue reduction diet among nine DLBCL survivors including specific fruits, vegetables, whole grains, and omega-3 fatty acid rich foods. This led to significantly improved diet quality and reduction in fatigue [98•]. More importantly, these techniques have been shown to improve patient empowerment and enable them to help themselves in an active way [99]. Finally, primary data have shown that CIM may even be associated

with prolongation of life in cancer survivors, although not specifically evaluated in lymphoma [100].

Therefore, different CIM modalities, mostly mind-body and nutrition, seem helpful in the symptomatic management of lymphoma survivors (Table 1) although further studies should confirm these data and evaluate their effects on other outcomes.

Safety

Although most CIM modalities, including acupuncture, are considered safe in patients with lymphoma [101••], one should be aware of the safety issues related to the use of herbal supplements in this setting, including potential side effects and herb-drug interactions [7]. These interactions seem to be more frequent among patients treated with specific chemotherapies, such as cyclophosphamide or vinca alkaloids [7]. The potential for interactions is notable considering the dramatic increase of novel therapies for lymphoma. For example, Bruton tyrosine kinase inhibitors, which are widely used for the treatment of low-grade lymphomas, are metabolized in the cytochrome P450 enzyme system and are therefore prone to interactions with drugs and dietary supplements inhibiting/activating this enzyme [102], such as the previously cited EGCG [103]. This should encourage implementation of a clinical pharmacist consultation before prescribing such herbs, as well as the importance of patient-practitioner communication regarding the use of supplements [104••].

Conclusions

Integrative hematology is a developing discipline, and CIM modalities are particularly important in the management of patients with lymphoma. Some data are revealed on the effect of nutrition and some dietary supplements on prevention and disease course, while most of the facts show the impact of different CIM modalities on symptom alleviation both during treatment and after remission. This review calls for more studies that should be designed to provide evidence-based guidelines for the integrative management of lymphoma in terms of effectiveness and safety and guide the hematologists in the clinic regarding the implementation of such interventions. Finally, a better patient-practitioner communication and systematic evaluation of potential safety issues should be emphasized in this population at high risk for complications.

Declarations

Conflict of Interest Authors have no conflict of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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