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Introduction to Hematologic Diseases and Integrative Therapies: The Use of Natural Supplements and Complementary Therapies with Clinical and Preclinical Evidence

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Abstract

Hematological diseases include benign and malignant conditions, some of which may have poor prognoses. Conventional treatments have helped to improve overall survival. However, they are often associated with numerous side effects that are not always manageable. Patients are increasingly seeking help from natural substances, mind-body activities or vitamins. Whether laboratory, preclinical or patient-based, scientific research has shown interesting data using these methods, which fall under the umbrella of Integrative Hematology. Curcumin, epigallocatechin, sulforaphane, melatonin, yoga, and mindfulness are just some of the natural products and mind-body methods whose scientific results we have evaluated. However, further clinical studies must be carried out before these methods can be considered as recommendations for use in the course of haematological pathology.

Keyword: Leukemia; Myeloma; EGCG; Vitamins

Introduction

Overview of Hematologic Diseases

Hematologic diseases include a wide spectrum of pathologies, ranging from benign degenerative forms to malignant neoplastic forms, affecting all the components of the blood. They affect blood production and regulatory systems: bone marrow, lymph node structures, and organs such as the spleen. Among the malignant forms, leukemia, lymphoma, and myeloma are the most prominent, each with its own characteristics. Lymphomas mainly affect the lymph nodes, spleen, lymphatic structures of various organs (only for example, thyroid, lung, stomach). Leukemia affects the bone marrow and causes overproduction of various blood components: white blood cells (myeloid line), red blood cells (erythroid line), lymphocytes (lymphoid line). Myeloma is primarily a proliferation of plasma cells that can affect both the bone marrow and all structures of the body in a localized or diffuse fashion. While benign forms of hematologic pathology respond to treatments related to the underlying cause of the disease (forms of anemia are resolved by acting on the underlying cause), neoplastic forms require specific chemotherapy, immunotherapy or targeted therapy to achieve positive resolution of the neoplasm. These neoplastic diseases have a significant impact on the quality of life and survival of patients and are a major cause of morbidity and mortality worldwide. A different approach is maintained between those who deal with oncology and those who deal with hematology because these two dimensions, although seemingly similar, are distant for numerous reasons. First of all, hematological cancers not only have an immune dysregulation that is common to all cancers, but are also characterized by an intrinsic alteration of immune function that is related to the fact that neoplastic cells often coincide precisely with cells of the immune system. Second, a large proportion of hematologic diseases have a better prognosis. Oncological treatments on Hodgkin's lymphoma give a very high median survival at 5 aa (over 70%) or as some indolent lymphomas such as chronic lymphatic leukemia or Waldestrom's M. that show a survival over a decade; in some cases patients with some types of lymphoproliferative diseases have the same survival expectancy as the healthy population (essential thrombosis or polycythemia vera) [1].

Limitations of Conventional Therapies

At the same time, we know that antiblastic therapies for both solid and hematologic cancers are associated with a number of adverse effects that often lead to reduction or discontinuation of drug administration. Indeed, despite significant advances in conventional therapies such as chemotherapy, radiation therapy and, in some cases, immunotherapies, many patients continue to experience a range of debilitating side effects, drug resistance and frequent relapses. Treatment can lead to immunosuppression, increased susceptibility to infection, anemia, impaired kidney and liver function, and an overall decline in quality of life.

Importance of Integrative Therapies

Given the complexity of these diseases and the impact of conventional treatments, there has been a growing interest in integrated therapies that combine standard protocols with scientifically supported complementary interventions. These approaches include the use of natural supplements that have been shown to have positive effects on cancer cells or related symptoms, potentially improving patients' quality of life and reducing some of

the side effects of conventional therapies. And this has also been seen in the case of hematology treatments, which indicates that this approach is called Integrative Hematology [2], used to define a multisystemic approach to blood diseases that not differs from integrative oncology in fact, blood cancers often have very not different biological and clinical features from those characterizing solid tumors [2-3]. Unfortunately, in many cases, available data are only in preclinical, *in vitro* and on animal models, while there are currently few clinical trials ongoing or concluded that involve the use of these substances in hematological patients. These data could be an incentive to help us to identify which one of the available remedies is the most useful and urgent to test in daily clinical practice.

The use of integrative medicine methods, which can be used in a scientifically sound manner to add value to conventional therapy without compromising its efficacy, is the subject of this chapter. In a general and very illustrative way, we will distinguish between hematologic diseases of the myeloid (myeloproliferative) and lymphoid (lymphoproliferative) lineages: from both groups we will examine some examples.

Myelodysplastic Syndromes (MDS) are a miscellaneous group of diseases characterized by an ineffective myelopoiesis linked to clonal dysplastic aspects of the stem cell and a consequent caratterizzate da anemia, piastrinopenia e leucopenia (peripheral pancytopenia). They can often give rise to damage to organs such as the heart and the circulatory system. Generally not responsive to growth factors and also characterized by transfusion refractoriness. These diseases are far more frequent in the elderly, affecting 1 in 3000 people over 70 years old. They can evolve into acute myeloid leukemia. In a low risk patients we should treat the anemia. Treatment for high-risk patients hypomethylating agents such as azacitidine is indicated. To treat other patients, if eligible, allogeneic stem cell transplantation should be taken into consideration as it is the only potentially curative tool to date [4].

As natural agents we could be use some plants

Curcumin (CUR): The active ingredient in the traditional herbal remedy and dietary spice turmeric (Curcuma longa). Curcumin has a surprisingly wide range of beneficial properties, including anti-inflammatory, antioxidant, chemopreventive and chemotherapeutic activity, is a commonly used chemosensitization agent for various types of tumors, including hematopoietic malignancies. Co-treatment of the cells with CUR and ATO (arsenic trioxide) resulted in significant synergistic effects in MDS cell downregulating the expression of survivin [5]. Some *in vitro* and *in vivo* studies have demonstred that curcumin can significantly suppress cell proliferation and induce cell apoptosis and cell cycle arrest in human MDS-derived cell lines by a lot of mechanisms (EZH2, DNMT3a, ASXL1, H3K4me3 and HOXA9 expression) [6]. Curcumin also showed anti-cancer effects in a xenograft mouse model and reduced EZH2, H3K4me3 and H3K27me3 *in vivo* and attenuates leukemic transformation *in vivo* [6].

Coenzyme Q10 (CoQ10): Some evidence suggests the efficacy of CoQ10, at a dosage of 1200 mg/daily, in causing not only hematological but even cytogenetic remissions [7]. The rationale for using this substance is that plasma CoQ10 concentration decreased in an untreated MDS group compared to controls; this could be related to the mitochondrial dysfunction and systemic inflammation [8]. Furthermore, its known antioxidant action could contribute to its effectiveness. A more recent study showed, in fact, a significant impairment of mitochondrial respiration in peripheral blood cells in low-risk MDS; the utilization of CoQ10 and carnitine improved not only mitochondrial function but also cytopenia and quality of life [9]. It is currently unclear which patient setting could benefit most from this substance but, given the lack of side effects, we believe it makes sense to use it in all patients with myelodysplastic syndrome, also in consideration of anecdotal data on marked improvement in patients with sideroblastic anemia and mitochondrial myopathy [10].

Vitamin K2: Vitamin K2 has been shown to improve cytopenia in this patient setting. By acting on the SXR receptors present on myeloid cells, it stimulates their differentiation (confirmed by an increase in CD11b and CD14); it would also have an antiapoptotic effect on erythroid cells [11]. A multicenter phase II trial demonstrated an improvement in anemia and/or thrombocytopenia in patients with low- or intermediate-1-risk MDS, using vitamin K2 for 4 months, where the improvement was enhanced by the addition of vitamin D3 and inversely proportional to the values of hemoglobin, confirmed in a recent meta-analysis [12]. The relationship between vitamin K and hematopoiesis has recently been confirmed by the observation that the use of vitamin K antagonists can compromise the bone marrow microenvironment, possibly with increased MDS risk [13].

Vitamin D: Pardanani et all. investigated the incidence of deficiency and prognostic impact of low levels of this hormone in myelodysplastic disease: 29% of MDS patients had insufficient vitamin D levels (<25 ng/mL), but these were not correlated with worse Overall Survival (OS) or Leukemia-Free Survival (LFS) [14]. However, more recent evidence shows a prognostic impact of vitamin D dosage at diagnosis and prior to azacitidine therapy: the probability of OS at 2 years in the low vitamin D group (<32.8 nM) would be 14% versus 40% in the high vitamin D group (>32.8 nM); according to this analysis, vitamin D would have a predictive value for worse survival in multivariate analysis independent of cytogenetics. Vitamin D supplementation would be suggested by *in vitro* evidence of a synergistic effect of the hormone with azacitidine itself [15]. Finally, some data seem to show that even in the absence of a true therapeutic response, vitamin D supplementation contributes to reducing the progression of acute leukemia, probably because of its differentiating properties [16].

Eicosapentaenoic acid: Given the finding of high levels of TNF-_ and IFN- in patients' seru it seemed logical to try the use of eicosapentaenoic acid together with docosahexaenoic acid, known for their effect of reducing these inflammatory cytokines. Two interesting case reports of patients with MDS that was refractory to previous treatments (including cyclosporine) show not only a reduction in serum cytokine levels but, in keeping with this, also a marked increase in the patients' hemoglobin (up to 2 g/dL), which did not occur in patients in whom the cytokines were not simultaneously reduced [17].

Melatonin: Melatonin works well in regolatory effect in blood cell proliferation in particular, its ability to increase hemoglobin and platelets in conditions in which cytopenia was also due to different causes [18]. There are some evidences that, also in patients with myelodysplasia secondary to chemotherapy, melatonin improved thrombocytopenia and neutrophil counts with a prolongation of survival in two of the six patients enrolled [19]. Melatonin is able

to promote hematopoietic stem cell self-renewal [20], but also protects stromal niche cells against toxic side effects of Reactive Oxygen Species (ROS) [21].

Withania Somnifera: We know for a long time the antineoplastic role of withaferin A (steroid lactone of this oriental plant); first study that documents it dates back to 1958 [22]. Leukemia and myelodysplastic cells, compared to other cancerous cells, are more sensitive to its action; in particular, the substance suppresses the growth of dysplastic and leukemic cells at doses well below those necessary in other cell types, but it also allows the mechanism of autophagy (by stimulation of HMOX1), which is presumed to be responsible for the chemoresistance mechanism. Therefore, despite the important suppressive effect on the cell growth of dysplastic cells, the same should be better studied in association with autophagy inhibitors [23].

Acute myeloid leukemia (AML): The second most common form of leukemia by incidence; its incidence increases with age, being very common in the elderly (where it accounts for all cases) and rare in children (<10% of cases). It is more common in males. There are several risk factors such as cigarette smoking or environmental Some genetic diseases (Fanconi anemia, Bloom's syndrome, ataxia-telangiectasia, Li-Fraumeni syndrome, neurofibromatosis, etc.), some chromosomal abnormalities (Down syndrome, trisomy of chromosome 8) and some blood diseases (chronic myeloproliferative disorders and myelodysplastic syndrome) may also increase the risk. It is a clonal disorder of stem cells characterized by altered proliferation of cells in the differentiated phase (myeloblasts) and failure of various lineages to mature, resulting in peripheral pancytopenia. The choice of the most appropriate therapy depends on the characteristics of the disease and the patient. The standard treatment consists of induction chemotherapy to achieve complete remission, i.e. the absence of signs and symptoms (less than 5 percent blasts in the bone marrow, normal blood counts and no clinical signs of leukemia), followed by consolidation chemotherapy, which aims to reinforce the results of the first phase by eliminating even the last remaining tumor cells. This is followed by allogeneic stem cell transplantation if the patient is eligible. In elderly or ineligible patients, targeted therapy (including the use of azacitidine and venetoclax) is the first choice. We also have other drugs, such as tyrosine kinase inhibitors (anti-FLT3) and monoclonal antibodies directed against a surface molecule (CD33), whose use in first-line therapy can improve the prognosis of the disease. However, this disease has a poor prognosis, with OS ranging from 5 to 21%. Based on these data, an attempt was made to analyze how natural compounds could provide therapeutic benefit in this setting.

Epigallocatechin-3-gallate (EGCG): The antiproliferative effect of EGCG on leukemic blasts has long been known [24]. Recently, another interesting aspect has been discovered: the suppression of blasts demonstrated *in vitro* is accompanied by inhibition of FLT3 expression. Since this subtype is associated with a poor prognosis, such an effect, which is only observed in mutant and not in wild-type cells, could certainly lead to promising developments [25]. A significant increase of death-associated protein kinase 2 (DAPK2) levels was found in AML cells upon EGCG treatment paralleled by increased cell death that was significantly reduced upon silencing of DAPK2. Epigallocatechin-3-O-gallate (EGCG), induces apoptosis cells through acid sphingomyelinase activation. EGCG activated the Akt/eNOS axis, a well-known mechanism in vascular cGMP upregulation. In animal models, EGCG also protects cardiomyocytes from doxorubicin toxicity. Micellar complexes containing EGCG and doxorubicin have been designed not only to bypass anthracycline cardiotoxicity, but also to overcome chemoresistance of leukemic cells due to EGCG's modulatory effect on P-glycoprotein activity [26]. An important observation is that EGCG has a marked effect on promyelocytic leukemia cell lines and shows a synergistic effect with trans-19 retinoic acid [27] suggesting that it may also play a role in this otherwise distinct subtype of the disease.

Ascorbic Acid (AA): The now dated finding that leukemic cells depend on AA to survive had led to discouragement of its use; however, this finding contradicted earlier findings by Pauling and Cameron showing that AA administration was effective in improving survival in cancer patients, even up to 20-fold over controls in some patients [28]. Against this controversial background, new studies have concluded that the antitumor effect is extrinsic through a paradoxical pro-oxidant action against neoplastic cells, an action opposite to that occurring factors such as exposure to certain chemicals such as benzene and its derivatives used in the chemical industry and refineries. Certain cancer treatments, such as alkylating and platinum-based drugs used in chemotherapy and radiation used in radiotherapy, also increase the risk of developing AML.

in normal cells. AA induces H2O2-mediated apoptosis at very low doses (<5mMol), whereas normal cells are insensitive to this effect even at doses of 20 mM, probably due to a difference in cellular permeability to extracellular H2O2 as well as the characteristic absence of catalase in leukemic cells. These preclinical data, added to the clinical data, although still limited, of the efficacy of AA in some patient settings and the absence of major side effects even at high doses [29], stimulate the use of AA by intravenous administration even in patients with AML. Evidence of synergy with decitabine in improving OS adds to these data [30].

Curcumin: The potent and eclectic antitumor activity of curcumin is also confirmed in acute myeloid leukemia, where it adds its important chemosensitizing role. Curcumin has also demonstrated good hypomethylating activity in myeloid leukemia cell lines, which translates into a reduction of tumor growth in *in vivo* models. In leukemic stem cell lines (associated with worse prognosis and typically present at the time of relapse) that are insensitive to daunorubicin, curcumin induces cytotoxicity by inducing apoptosis through reduction of BCL2 expression, the overexpression of which contributes to the chemoresistance of these cells, while sparing normal hematopoietic progenitors from this effect, a fact that should be emphasized [31]. Busulfan (a drug widely used in stem cell conditioning regimens prior to transplantation) also shows little activity against these CD34+ chemoresistant leukemic cells, but curcumin has been shown to increase busulfan-induced apoptosis. The authors of the study suggest that this synergistic effect may allow a reduction in the required clinical dose of busulfan, with the aim of reducing mortality related to transplant toxicity: this is precisely one of the goals of integrated onco-hematology, i.e. to minimize the required chemotherapy and thus the toxicity to the patient by exploiting the synergistic effect of nutraceuticals, but not only those that are available to us [32].

Resveratrol: This molecule is capable of sensitizing numerous neoplastic cells to chemotherapeutic agents such as vincristine, adriamycin, paclitaxel, doxorubicin, cisplatin, gefitinib, 5-fluorouracil, velcade, and gemcitabine. The chemosensitization of tumor cells by resveratrol appears to be mediated through its ability to modulate multiple cell-signaling molecules, including drug transporters, cell survival proteins, cell proliferative proteins, and members of the NF-κB and STAT3 signaling pathways [33]. There are numerous *in vitro* studies on the action of resveratrol during acute myeloid leukemia. The actions of the compound concern ferroptosis, apoptosis in its various activation pathways, cell cycle arrest, senescence action of neoplastic stem cells, blockade of the NFKb transcription pathway, inhibition of proliferation, S-phase arrest, sensitizes to HDAC inhibitors, down regulates IL6 and IL1-b [34-37]. In HLA-60 cell line was seen to induce MDR activity (MPR1) [38], while in AMC cell lines was shown to down regulate MPR1 to doxorubicin [39]. Clinical studies are needed to understand whether the compound can be safely used in this hematologic disease.

Lymphoproliferative diseases

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most common form of leukemia in the Western world, with a peak incidence between the ages of 60 and 70. Only 15% of patients are younger than 60 at diagnosis. It is characterized by clonal expansion of a mature B lymphocyte that accumulates in the peripheral blood and lymphoid organs (spleen and lymph nodes) in 95% of cases, followed by variable splenomegaly and lymphadenopathy. The disease has a very heterogeneous clinical course: diagnosis is often incidental, and some patients remain symptomatic and stable for years without any therapy, while others develop symptoms early and have progressive disease. It is precisely because of the often indolent or otherwise slow course of the disease that chronic lymphocytic leukemia stands out as a disease in which the integrated approach can be an "opportunity to add therapeutic value to the drugs already in use, thanks to the use of substances that often take longer to act but are proving so effective that we can no longer shy away from considering them.

Curcumin: In CLL B lymphocytes, there is evidence of constitutive activation of NFkB: therefore, the use of this spice may have a rationale in this disease as well. Studies confirm its apoptotic effect in CLL B cells with a parallel reduction of NFkB. Curcumin also increases the levels of vincristine-induced apoptosis in these cells. Beyond the preclinical data, it is interesting to point out the presence in the literature of a case report in which a complete remission, hematologic and molecular (persisting after 3 years), was achieved with the use of curcumin and EGCG alone [40] because of their synergistic action. The evidence of synergy documented by these two articles led to the publication of an editorial with the catchy title "Turmeric and green tea: a prescription for B-CLL", in which it is shown how the two substances have some common mechanisms of action, but each also has its own specific mechanisms that increase the benefit of the use of both [41]. The synergistic effect of curcumin in combination with doxorubicin has also been demonstrated *in vivo* in aggressive B lymphomas.

EGCG: Green tea consumption was inversely associated with the risk of developing lymphoproliferative neoplasms in a 9-year cohort study of 42,000 individuals [42]. Early anecdotal evidence of spontaneous remissions in patients taking this supplement [43] paved the way for two phase I and II clinical trials of a standardized green tea extract in asymptomatic CLL patients with Rai stage 0-1. The first study showed good tolerability up to the highest doses (4 g per day) and a reduction of lymphocytosis and lymphadenopathy in the majority of patients [44]. The subsequent phase II study with the same extract dosage showed an overall response rate of 70%, regardless of patient prognostic factors. Although it is unclear whether these satisfactory results will translate into slowing disease progression or delaying the initiation of chemotherapy in the future, this is certainly very promising evidence [45].

Resveratrol: Resveratrol also shows in this disease to be able to give a cytotoxic effect (cell cyst arrest) to CLL cells [46]. In addition, it is able to induce apoptosis in B lymphocytes from CLL patients, sparing normal ones, and shows synergism of action, *in vitro*, with purine analogues such as fludarabine. These findings are greater in cells from patients with positive prognostic factors or limited disease, suggesting that this compound may play a more significant role in early stages of disease or in disease with a better prognosis [47].

Vitamin D: The results of the EPIC study do not show an inverse association between vitamin D levels and lymphoproliferative diseases in general; however, the same analysis shows that CLL in particular breaks away from this trend and higher levels of vitamin D in the blood are associated with a reduced risk of developing the disease [48]. Low vitamin D levels in these patients are also associated with CD38 positivity and a more advanced stage of the disease, and in a multivariate analysis it is indeed shown to be an independent negative prognostic factor in CLL [49]: its dosage should therefore be recommended at the time of diagnosis and used together with the other prognostic factors to outline the patient's therapeutic strategy, also in view of the evidence that lower levels correlate with a shorter time to treatment (TTT) and reduced OS [50]. In this case, vitamin D would be the only modifiable prognostic factor of the patient at diagnosis.

Melatonin: It is very interesting to note that an association has been observed between the incidence of CLL and alterations in circadian rhythms. In particular, there appears to be a greater likelihood of developing CLL in workers who work rotating night shifts, especially after 20 years of work (51). This finding, coupled with the finding of low melatonin levels in patients with CLL, underscores the role that this substance may play in this pathology.

Multiple Myeloma/Monoclonal Myeloma of Uncertain Significance (MGUS)

Monoclonal gammopathies: These are characterized by abnormal proliferation of plasma cells in the bone marrow, resulting in increased production of an antibody protein called the Monoclonal Component (CM), which consists of an antibody, most commonly IgG, which is mild (<10% bone marrow plasma cells) in the case of MGUS (Monoclonal Gammopathy of Uncertain Significance) or frankly pathological (>10% bone marrow plasma cells) in the case of Multiple Myeloma (MM). The disease accounts for 10% of hematologic diseases, second only to non-Hodgkin's lymphoma: it is more common in the elderly, while only 2% of patients are younger than 40 years at the time of diagnosis: in these cases, unfortunately, the disease already shows a more aggressive course at presentation. The production of inflammatory cytokines by the

neoplastic cell, together with the expansion of the bone marrow itself, is the cause of the osteolytic lesions typical of the disease and of one of the main symptoms, bone pain; other characteristic symptoms are renal failure (as a consequence of excess serum protein and hypercalcemia) and anemia. At present, multiple myeloma continues to be a disease with a poor prognosis, with an overall survival rate at 5 years of less than 20%.

Curcumin: This substance, the use of which has become indispensable in neoplastic patients, also shows some remarkable specific effects in MM: first of all, inhibition of NFkB, in addition to that already used in practice with the use of bortezomib, demonstrating how the regulation of this pathway has given an advantage in terms of response precisely in MM.

It also downregulates IL6, a key cytokine in this disease, and inhibits osteoclastogenesis by inhibiting RANKL. In *in vitro* and murine models, it increases chemosensitivity to dexamethasone, doxorubicin and melphalan and synergizes with the effects of bortezomib and thalidomide. It also has potent anti-apoptotic activity in MM cell lines harboring translocations associated with poor prognosis (t4;14 et14;16). Although there are very few clinical trials testing natural products in hematology, as many as two specifically involve curcumin in monoclonal gammopathies. The first study involved 26 patients with MGUS treated with 4 g/day of curcumin and showed a reduction in the monoclonal component in 50% of the patients, where this was of reasonable magnitude (>2 g/dL), in parallel with a reduction in markers of bone resorption [52]. This promising clinical trial paved the way for a double-blind, randomized trial versus placebo in both MGUS and smoldering myeloma (a gray zone condition in which plasma cells are >10% but the peripheral picture is normal, and with a 3% annual risk of progressing to frank myeloma). Curcumin at both 4 and 8 g doses reduced the k/λ ratio (a parameter reflecting disease burden, response to therapy, and prognosis) by 35 and 36 percent, respectively, as well as bone resorption markers [53]. Although few cases of MGUS and smoldering myeloma progress to full-blown disease, it is precisely for this reason that the use of conventional chemotherapy is not justified in these cases; instead, curcumin can unfold its full chemopreventive potential in this setting.

Sulforaphane: This cruciferous isothiacyanate has been shown to have similar activity to bortezomib in inhibiting IkB (proteasome inhibitor) degradation and ultimately shows synergy with dexamethasone, doxorubicin, bortezomib and melphalan. In animal models, it reduces disease burden and prolongs survival [54].

Epigallocatechin-3-gallate (EGCG): The apoptotic effect of EGCG on MM cells appears to result from the stimulation of ROS and the reduction of peroxiredoxin (antioxidant molecule) levels, as well as a selective interaction with laminin receptor 1, which is much higher in MM patients than in controls, and the absence of which abolishes the apoptotic effect of EGCG (55). The interaction of EGCG with bortezomib has been studied and is controversial: two contradictory scientific papers were published in 2009, a few months apart. The first claimed the ability of EGCG to antagonize the effect of Bortezomib in inhibiting the proteasome both *in vitro* and *in vivo* models, at concentrations easily obtained even in humans, to conclude by dissuading the association of the two substances. That is, although EGCG is able to inhibit the proteasome, this would not be the case in the presence of bortezomib, where it would prevent its action, perhaps by binding to the molecule's boronic acid (56). In the second paper, however, this assumption was refuted by evidence of a synergistic effect between the two substances, which, according to the authors, was due to a higher dosage of EGCG and bortezomib used (57). These data raise several considerations: first, the risk that *in vitro* studies may not reflect what really happens *in vivo*, given the different and often unquantifiable concentrations that the substance takes up inside the cell, depending on many variables, including uptake and bioavailability. In addition, one should never forget the possibility that substances from the plant world may have undesirable effects or interactions with other drugs, so it is imperative to be aware of them and know how to deal with them. In this particular case, the prudent attitude adopted has led us to discourage the use of EGCG in combination with bortezomib, an attitude that has been reaffirmed, among other things, by a recent study on prostate cancer cells in which the antagonism between the two appears again (58).

Resveratrol: Resveratrol, in addition to inhibiting apoptosis and enhancing the effect of Bortezomib, also has a marked anti-angiogenic effect by regulating various factors such as VEGF, bFGF, MMP2 and MMP9. It also inhibits the constitutive activation of STAT3 and NFkB, overcoming an important mechanism of chemoresistance and again synergizing with bortezomib and thalidomide [59]. It must be remembered, however, that high doses of resveratrol (5gr/day) may cause alterations in liver enzymes or renal toxicity [60].

Vitamin D: Even in MM, there seems to be a relationship between this hormone and the likelihood of disease onset: patients with MM have a higher vitamin D deficiency, and this deficiency appears "alarmingly" in patients with bone lesions [61]. The already known correlation between low vitamin D levels and increased PCR, which has also been confirmed in MM patients, makes it an additional negative prognostic marker: lower levels are indeed also associated with a more advanced stage at diagnosis [62]. Bortezomib itself also seems to act at this level: it increases osteoblast differentiation by upregulating VDR production, and its effect is enhanced by the addition of vitamin D. The severity (but not the incidence) of peripheral neuropathy from drugs such as bortezomib itself or thalidomide is also related to vitamin D deficiency, which should therefore be even more appropriately dosed and corrected before starting therapy with these types of drugs [63].

Cannabinoids: Cannabinoids are natural compounds found in the cannabis plant with effects in chronic pain and chemotherapy-induced nausea and vomiting [64]. In MM, *in vitro* studies have shown reduced myeloma cell viability and proapoptotic activity. in cannabinoid-treated MM cells, even in those resistant to dexamethasone cannabinoids are able increasing the efficacy of the second-generation immuno-proteasome inhibitor carfilzomib. Moreover, they allow resistance mechanisms actually linked to the expression levels of 5i to be overcome [65]. These compounds are promising not only in improving the symptoms and quality of life of patients, but also for their antitumor and synergistic activity with currently used drugs.

Complementary Therapies

Yoga

The practice of yoga combines physical postures, breathing techniques and meditation, and has been associated with several health benefits, particularly in reducing stress and pain, improving quality of life in cancer patients. Several meta-analyses have shown that yoga is effective in improving quality of life and reducing fatigue in cancer patients [66]. Specific studies suggest that yoga may reduce anxiety and depression and contribute to an improved overall psychological state in patients with haematological diseases. The data reviewed did not reach a clear and significant conclusion [67]. Further in-depth studies are needed to define the true value of the therapy in the haematological field.

Mindfulness

These techniques, which include meditation and mindfulness, focus attention on the present moment and have been shown to reduce stress and improve psychological well-being. Studies have shown that mindfulness programmes can significantly reduce anxiety and improve quality of life in cancer patients, helping them to cope with symptoms related to the disease and treatment [68].

Diet

A balanced diet is essential to support general health and the immune system, particularly in patients with haematological disorders. Certain nutrients, such as antioxidants and omega-3 fatty acids, may have a beneficial effect on disease control and response to treatment. Research suggests that a diet rich in fruits, vegetables, and whole grains is associated with better outcomes in cancer patients. Some studies have shown that supplementation with anti-inflammatory foods may improve treatment response and reduce side effects [69]. Dietary recommendations based on scientific evidence are also available for haematological patients [70].

Aromatherapy

Aromatherapy uses essential oils to promote physical and mental wellbeing. It has been used to relieve anxiety, nausea and pain, making it a popular choice among cancer patients. Several studies have shown that aromatherapy can reduce anxiety and improve sleep quality in cancer patients, contributing to overall support during treatment [71]. A study of paediatric patients with nausea and vomiting during chemotherapy showed a significant reduction in symptoms with peppermint and lemon inhalation [72].

Massage and Physical Activity

Massage therapy is known for its ability to reduce muscle tension, pain and anxiety. It is a practice that can be incorporated into the care of cancer patients to improve general wellbeing [73]. In terms of physical activity, it is not usually recommended because patients often have anemia or thrombocytopenia, although this limitation reduces quality of life. Many studies have shown that therapeutic massage can relieve pain and fatigue in cancer patients, improving their quality of life and contributing to recovery [74]. There is little significant evidence from trials on the safety, validity and effectiveness of physical activity, although improvements in fatigue and depression are apparent [75]. Data on quality of life, anxiety and physical improvement are inconclusive.

Conclusions

The supplementation of some natural supplements such as curcumin, EGCG, vitamin D, resveratrol, supported by solid preclinical and clinical evidence, offers significant support in the treatment of hematological diseases. These supplements have anti-cancer properties, anti-inflammatory and immunomodulatory properties that help control disease progression and improve patients' quality of life. The integration of complementary therapies such as yoga, mindfulness, nutrition, aromatherapy and massage into the treatment of haematological disorders offers significant potential to improve patients' quality of life and well-being. These approaches, supported by clinical evidence, can not only help to control disease but also improve response to conventional treatments, providing a more holistic approach to patient care.

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