Nutritional Support for Chronic Myelogenous and other Leukemias: A Review of the Scientific Literature

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Abstract

Chronic myelogenous leukemia (CML) is a slowly progressive disease characterized by the overproduction of granulocytes (neutrophils, eosinophils, and basophils). A blood smear shows moderate elevations in white blood cell counts that may persist for years and be benign. Platelets are increased in number, although their function is impaired, resulting in symptoms of easy bleeding (purpura, swollen gums). Conventional medical treatment is a marrow transplant and alkylating agents, which are usually prescribed only during crisis. Several nutrients and botanicals have been studied for use in CML, including vitamin A and all-trans retinoic acid (Retin-A), vitamin D3, vitamin E, vitamin B12, indirubin (found in herbs including *Indigofera tinctoria* and *Isatis tinctoria*), and *Curcuma longa*. This article briefly reviews the scientific literature on the therapeutic use of these nutrients for CML.

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Introduction

Chronic myelogenous leukemia (CML) is also referred to as chronic myeloid, chronic myelocytic, and chronic granulocytic leukemia. CML is a clonal proliferation caused by malignant transformation of a pluripotent cell. Marrow invasion occurs, leading to increased red and white blood cells and platelet counts. Symptoms of CML include fatigue, purpura, hives, swollen gums, pruritis due to histamine release, and chloroma (red-brown skin papules that become green when blood is squeezed out). Signs include anemia and splenomegaly. A blood smear will show moderately elevated white blood cells (mostly myelocytes), which may persist for years and be benign. Basophils are elevated and marrow mast cells are increased. Although platelets are increased in number, their function is impaired. Serum B12 levels are markedly increased, and uric acid levels are elevated. The clinical course of CML is slowly progressive, with disease acceleration defined by the development of increasing anemia unaccounted for by bleeding or chemotherapy, cytogenetic clonal evolution, blood or marrow blasts ≥15 percent but <30 percent, promyelocytes ≥30 percent, blood or marrow basophils ≥20 percent, or platelet count <100,000/uL. A blast crisis (acute leukemia) is defined as blood or marrow blasts ≥30 percent. Median survival is approximately 40 months. Cigarette smoking, which induces leukocytosis, has been shown to accelerate the progression to blast crisis and therefore has an adverse effect on survival.[1,2]

Etiological Factors

Chronic myelogenous leukemia is associated with chromosomal damage that may be caused by ionizing radiation. The translocation of chromosomes is believed to play a central role by forming BCR-ABL fusion proteins that have been shown to transform hematopoietic progenitor cells *in vitro*. Incidence of CML is increased in patients with Down's syndrome (abnormal chromosome 21) and Philadelphia chromosome (translocation of an oncogene from chromosome 9 to chromosome 22).

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One study found a decrease in antioxidant defense and an increase in the level of lipid peroxidation in red blood cells of 56 patients with polycythemia vera (PV), CML, and chronic lymphoid leukemia (CLL) with and without anemia as compared with 50 healthy persons.[3]

Conventional Treatment

The goal of conventional treatment is palliation. With chemotherapy, the patient may be kept asymptomatic for long periods by keeping the white blood cell count below 50,000/uL. Several prescription medications may be used (Table 1).

Table 1. *Conventional Medications Used in the Treatment of Chronic Myelogenous Leukemia*

Hydroxyurea (Hydrea®) is currently the cytotoxic agent of choice. It blocks ribonucleotide reductase, impairing DNA (but not RNA) synthesis.
Busulfan (Myleran®) is an alkylating agent acting mainly on myeloid cells and hematopoetic stem cells; commonly used during the chronic phase.
Plicamycin (Mithracin®; Mithramycin) inhibits DNA synthesis and DNA-dependant RNA synthesis.
Vincristine (Oncovin®) is an antineoplastic agent approved for acute lymphocytic leukemia (ALL).
Interferon alpha (Alferon®; Intron®; Roferon®) is an immunomodulator that has been shown to produce remission with disappearance of Philadelphia-chromosome-positive cells in the marrow in some patients; but, the long-term benefit is not yet known.
Allopurinol may be recommended to reduce uric acid levels.

Research Studies

Tretinoin, ATRA, Retin-A

Several studies have been performed on all-trans retinoic acid (ATRA), also known as tretinoin (Retin-A, Renova, Vesanoid). ATRA is a naturally occurring derivative of vitamin A (retinol). Oral tretinoin is approved for use as a chemotherapeutic agent for acute promyelocytic leukemia (APL). ATRA, like other retinoids, induces cancer cells to mature, thereby eliminating abnormal proliferation, possibly by down-regulating expression of c-Myc, a gene involved in monocyte differentiation.[4,5]

An *in vitro* study published in the journal *Leukemia* described the effects of ATRA and interferon alpha on the growth of leukemic progenitors in cells from patients with newly diagnosed CML. While each alone provided inhibitory effects, combining the two provided a more dramatic inhibitory effect on the growth of granulocyte-macrophage colony forming units (CFU-GM). These results suggest the combination of interferon alpha and ATRA may be of potential interest for the treatment of CML.[6]

A review article published in the journal *Haematologica* described the results of a Chinese group working in Shanghai. The researchers found

94 percent of acute promyelocytic leukemic patients obtained complete remission through differentiation of the leukemic clone, with ATRA alone.[7]

A study in *Leukemia Research* examined ATRA in patients with advanced stage CML (in accelerated phase or blastic crisis). CFU-GM from patients with advanced stage CML were inhibited by ATRA approximately 1000-fold more potently than those from chronic phase. Similar effects were seen with 13-cis-retinoic acid.[8]

Treatment with ATRA induces leukemic cells to differentiate, but is associated with many side effects. ATRA syndrome is related to high white blood cell counts, and includes fever, dyspnea, pleural and pericardial effusion, and hypotension. Chemotherapy acts by killing leukemic cells, which release procoagulants that can produce disseminated intravascular coagulation. As such, chemotherapy and ATRA appear to have opposite effects on leukemic cell counts and are often combined to reduce mortality.[9,10]

A pilot study used ATRA to treat 10 cases of advanced adult chronic myelomonocytic leukemia (CMML). The researchers found in some cases of CMML, ATRA improved anemia or thrombocytopenia, but not other parameters. Furthermore, it can also induce hyperleukocytosis and ATRA syndrome in some patients, which can be reversed by the addition of hydroxyurea.[11]

Vitamin A

A multi-center trial of vitamin A was conducted on patients with CML in chronic phase. A total of 124 patients completed the seven-year trial. Subjects were randomized to receive oral pulse busulfan (n=67) or busulfan plus continuous oral vitamin A at a dose of 50,000 IU daily (n=57). Adjustments were made in the vitamin A dosage depending on side effects and serum vitamin A levels. Patients in the busulfan plus vitamin A cohort had somewhat longer durations of clinical progression-free survival (median 46 months) and overall survival (51 months) compared to those in the busulfan cohort (medians 38 and 44 months, respectively). Although these results did not reach statistical significance, they are clinically significant. Moderate, generally tolerable, doses of vitamin A may favorably impact treatment of CML with alkylating agents.[12]

The authors of the study speculated on potential mechanism involved in vitamin A therapy including: (1) enhancement of cell-mediated immunity, seen in animal studies, (2) modulation of gene expression (especially during the blast phase), or (3) secondary response to increased plasma levels of busulfan (due to vitamin A's effect on liver metabolism).[12]

The *European Journal of Haematology* described an open study of 34 patients with myelodysplastic syndromes treated with vitamin A (13-cis-retinoic acid) at doses of 10-60 mg/m^2/daily) in combination with vitamin E, which was added to diminish side effects. Patients were treated with retinoids and vitamin E for a period ranging from three months to five years. Four patients, including two with CMML, experienced partial remission.[13]

Vitamin D

The *British Journal of Haematology* described a case of CMML treated with 25-hydroxy vitamin D3 (25-OH D3). The 72-year-old man with a poor prognosis for remission was treated with 16,000 IU 25-OH D3 three times weekly. Within one month his blood parameters were improving and 15 months later he remained in remission. At baseline his 25-OH D3 levels were below normal (4.2 ng/mL; normal 8-82) and 1,25 dihydroxy vitamin D3 (1,25(OH)2 D3) were low normal (19.9 ng/mL; normal 18-54). During treatment 25-OH D3 levels fluctuated between 35 and 202 ng/mL, while serum levels of 1,25 (OH)2 D3 and calcium remained normal.[14]

Vitamin D is involved in regulation of cell growth and differentiation, as well as the immune response. An *in vitro* study examined the effects of 1,25 (OH)2 D3 on a Philadelphia chromosome-positive CML cell line, RWLeu-4. Vitamin D3 induced 24R-hydroxylase activity (a marker of vitamin D3 responsiveness in many tissues), inhibited proliferation and DNA synthesis, and caused 50 percent of the cells to differentiate into macrophage/monocyte type cells.[15]

Two articles by Sokoloski et al discuss the differentiation of leukemic cells by antioxidants and anti-inflammatory agents, including vitamin E and curcumin. Vitamin E has been found to enhance leukemic cell differentiation in the presence of low levels of 1,25 (OH)2 D3.[16] Based on this information the research examined curcumin. Alone it had no effect but when combined with vitamin D3 it significantly enhanced expression of markers of cell differentiation. Curcumin with vitamin D3 appear to exert their effects by inhibition of transcription factor NF-kappa B, an effect that as been found to enhance leukemic cell differentiation.[16,17]

Vitamin E

Baseline serum vitamin E levels were measured in 25 patients with CML and 25 matched healthy controls and were found to be significantly lower in CML patients (2.67 mcg/mL). Vitamin E levels increased significantly after treatment with busulfan and hydroxyurea (3.61 mcg/mL), but remained lower than the controls (7.19 mcg/mL). The authors concluded the increase in vitamin E levels without supplementation could be due to a decrease in oxidative stress associated with a lower tumor load.[18,19]

Vitamin B12

Vitamin B12 is an essential coenzyme for DNA synthesis, although humans are incapable of synthesizing it. Vitamin B12 malabsorption may be caused by several mechanisms, including a deficiency of intrinsic factor or abnormalities in vitamin B12 binding proteins.

Elevation of vitamin B12 levels in CML was first reported in the 1950s.[20] Despite possible elevation in serum B12, however, people with CML seem to have a relative deficiency, which may be associated with abnormal binding proteins. One study measured serum vitamin B12 and vitamin B12 binding proteins (transcobalamin I and II) in patients with CML. The values of unsaturated vitamin B12 binding capacity of patients with CML were found to be higher than that of normal controls. A markedly increased transcobalamin I and decreased transcobalamin II were observed in patients with CML. The authors proposed this could be caused by increased granulocytes, the source of transcobalamin I, in patients with CML.[21]

Vitamin K

An article published in the journal *Leukemia* described a study of the apoptosis-inducing ability of vitamin K2 (menaquinone 3, 4 and 5; made by intestinal bacteria) and its derivatives such as phytonadione (vitamin K1), as well as polyprenylalcohols (which compose the side chains of vitamin K2), toward leukemia cells *in vitro*. Menaquinone 3, 4, 5 and geranylfarnesol (at 10 microM) showed potent apoptosis-inducing activity for freshly isolated leukemia cells, for an acute promyelocytic leukemia (APL)-derived cell line, and for a cell line derived from a patient with myelodysplastic syndrome. Vitamin K1, on the other hand, showed no effect on any leukemia cell lines tested. The combination of menaquinone 5 plus ATRA resulted in better induction of apoptosis in APL cells than either substance alone. This research suggests the potential of supplementation of vitamin K2 alone or in combination with ATRA for the treatment of myelogenous leukemias, including APL.[22]

Indirubin

Indirubin, extracted from botanicals, including *Indigofera tinctoria* and *Isatis tinctoria*, is the active ingredient of the traditional Chinese medicine formula Dang gui Long hui Wan, which is used for CML.[23-26]

Indirubin has been found to inhibit cyclin dependent kinases and glycogen synthase kinase-3. Aberrant expression of these proteins is involved in the G1 phase of the cell cycle.[27-32]

Studies of meisoindigo, an indirubin derivative, indicate it strongly inhibits DNA biosynthesis in tumor cells and inhibits the assembly of microtubules. Experimental results on the mouse leukemia L1210 cell cycle showed meisoindigo induced accumulation of S phase cells. The movement of cells in G2 + M phase to G1 phase may also be blocked to some extent.[33] Meisoindigo has been shown to down-regulate c-Myb, a gene required for progression in the S phase.[34]

Indirubin has also been shown to have an anti-inflammatory action by inhibiting the production of interferon-gamma, a well-known inflammatory cytokine.[35]

Curcumin

In addition to potentiating the effect of vitamin D, curcumins I and III exhibit *in vitro* cytotoxicity against human chronic myeloid leukemia in a dose dependent manner.[36]

Several studies have sought to identify the mechanism of action of curcumin on leukemia. Curcumin has been shown to inhibit experimentally induced apoptosis by inhibiting c-jun/AP-1 and bcl-2 (key modulators of apoptosis).[37,38] Interestingly, curcumin has also been found to promote apoptosis in a leukemia cell line. Because the effect was reversed by antioxidants including N-acetyl-L-cysteine, ascorbic acid, alpha-tocopherol, super oxide dismutase, and catalase, the research suggests apoptosis was mediated by oxidation.[39]

Curcumin has been shown to suppress the tumor promoter-induced activation of transcription factors, NF-kappa B (which is involved in regulation of cytokine synthesis) and AP-1.[40]

Conclusion

Several nutrients, botanicals, and their derivatives show promising effects in the treatment of chronic myelogenous leukemia. All-trans retinoic acid, vitamin A, and vitamin D3 have shown potential benefit in patients with CML. In China, the flavonoid indirubin is used to treat CML. *In vitro* studies show vitamin K2 and curcumin to inhibit CML cancer cell development. Patients with CML have been shown to be deficient in vitamin E and may have abnormalities in vitamin B12 metabolism. A decreased antioxidant status has also been found. Most nutrient research in CML is preliminary, warranting further study.

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