Nutritional Support for Chronic Myelogenous Leukemia,  
A Review of the Scientific Literature  

by Ronald Steriti, NMD, PhD

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 ankylosing agents, which are usually prescribed only during crisis. Several nutritional supplements have been studied for use in CML. These include vitamin A and all-trans retinoic acid (Retin-A), vitamin D-3, vitamin E, vitamin B12, Indirubin (from the Chinese herb from *Indigofera tinctoria* or *Isatis tinctoria*), and *Curcuma longa* (from the spice Turmeric). This article briefly reviews the scientific literature for the therapeutic use of these nutrients for CML.

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 blood cell, platelet and white blood cell counts.

Symptoms of CML include fatigue, purpura, hives and pruritis due to histamine release. Signs include anemia, purpura, swollen gums (due to cellular infiltrate), splenomegaly, and “chloroma” (red-brown skin papules that become green when blood is squeezed out).

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, blood or marrow blasts and 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]
**Cause**

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

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), chronic myelogenous leukemia (CML), chronic lymphoid leukemia (CLL) with and without anemia, and in 12 iron deficiency anemia patients, as compared with 50 healthy persons. [3]

**Conventional Treatment**

The goal of 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

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
<th>Note</th>
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<tbody>
<tr>
<td>Hydroxyurea (Hydrea)</td>
<td>is currently the cytotoxic agent of choice. It blocks ribonucleotide reductase, impairing DNA (but not RNA) synthesis.</td>
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<tr>
<td>Busulfan (Myleran)</td>
<td>is an alkylating agent whose activity is mostly seen in myeloid cells and hematopoietic stem cells. It was commonly used during the chronic phase.</td>
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<tr>
<td>Plicamycin (Mithracin, Mithramycin)</td>
<td>inhibits DNA synthesis and DNA-dependant RNA synthesis.</td>
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<tr>
<td>Vincristine (Oncovin)</td>
<td>is an antineoplastic agent approved for acute lymphocytic leukemia (ALL).</td>
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<tr>
<td>Interferon alfa (Alferon, Intron, Roferon)</td>
<td>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.</td>
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<tr>
<td>Allopurinol</td>
<td>may be recommended to reduce uric acid levels.</td>
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Research Studies

**Tretinoin, ATRA, Retin-A**

Several studies have been performed on all-trans retinoic acid (ATRA), also known generically as tretinoin (Retin-A, Renova, Vesnoid). 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 c-myc gene expression. [4] [5]

An article published in the journal *Leukemia* described a study of the effects of ATRA and interferon alpha on the growth of leukemic progenitors in CML. The addition of ATRA to interferon alpha dramatically potentiated the inhibitory effects of interferon alpha on CFU-GM growth. The authors concluded that, *in vitro*, the combination of interferon alpha and ATRA effectively inhibits CFU-GM colony formation in CML and suggest that it has a 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. Using ATRA alone, 94 percent of acute promyelocytic leukemic patients obtained complete remission through differentiation of the leukemic clone. [7]

An article published in the journal *Leukemia Research* described a study of ATRA in patients with advanced stage CML, i.e. in blastic crisis or accelerated phase. Granulocyte-macrophage colony forming units (CFU-GM) from patients with advanced stage CML were inhibited by ATRA approximately 1000-fold more potently than those from chronic phase.[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. ATRA syndrome includes fever, dyspnea, pleural and pericardial effusion, and hypotension. Chemotherapy acts by killing leukemic cells, which release procoagulants that can produce disseminated intravascular coagulation. Tretinoin is often combined with chemotherapy to reduce the mortality by preventing both syndromes. [9] [10]

A pilot study published in the journal *Leukemia* used ATRA to treat 10 cases of advanced adult chronic myelomonocytic leukemia (CMML). The researchers found that in some cases of CMML, ATRA can improve anemia or thrombocytopenia but not other parameters. Furthermore, it can also induce hyperleukocytosis and ATRA syndrome in some patients, requiring the rapid addition of cytoreductive agents such as hydroxyurea. [11]

**Vitamin A**

A cooperative group trial of vitamin A was conducted in 153 patients with CML in chronic phase. The CML patients were randomized to receive oral pulse busulfan (Myleran) or busulfan plus continuous oral vitamin A. Patients in the busulfan plus vitamin A arm had somewhat longer durations of clinical progression-free survival (median 46 months) and overall survival (51 months) compared to those in the busulfan
arm (medians 38 and 44 months, respectively). However, the differences were not statistically significant. The authors concluded that further investigation of retinoids in chronic phase CML is warranted. [12]

An article published in the European Journal of Hematology described a study of 34 patients with myelodysplastic syndromes treated with vitamin A (13-cis-retinoic acid, between 10 and 60 mg/m²/daily) in combination with vitamin E to diminish side effects. The duration of treatment was 3 months to 5 years. Partial remission was achieved in 4 patients. [13]

**Vitamin D3**

A report was published in the British Journal of Haematology described a case of chronic myelomonocytic leukemia (CMML) in whom a complete remission was achieved and sustained 15 months after treatment with 25-OH vitamin D3. [14]

An *in vitro* study examined the effects of vitamin 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% of the cells to differentiate into macrophage/monocyte type cells. [15]

Several articles by Sokoloski showed the differentiation of leukemic cells by antioxidants and anti-inflammatory agents (including vitamin E and curcumin) was significantly enhanced when combined with low levels of vitamin D3. [16] [17]

**Vitamin E**

Serum vitamin E levels were measured in 25 patients with CML and 25 matched healthy individuals (controls). Mean serum vitamin E levels were significantly decreased in CML patients before starting the treatment as compared to control. Vitamin E levels increased significantly after treatment with busulphan and hydroxyurea, but remained lower than the control. The authors concluded that this could be due to decrease in oxidative stress associated with a decrease in tumor load. [18] [19]

**Vitamin B12**

Elevation of the vitamin B12 level in chronic myelogenous leukemia was first reported in the 1950s. Vitamin B12 is an essential coenzyme for DNA synthesis. Humans (and other mammals), however, are incapable of synthesizing it. Vitamin B12 malabsorption may be caused by several mechanisms, including a deficiency of intrinsic factor, or a deficiency in vitamin B12 binding proteins, which may explain the elevated levels found in CML. [20]

Megaloblastic anemia due to vitamin B12 deficiency is a reversible form of ineffective hematopoiesis. It has been proposed that some forms of myeloid leukemia may resolve with vitamin B12 treatment. [21]

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 the normal controls. A markedly increased transcobalamin I, and decreased transcobalamin II was
observed in patients with CML. The authors proposed that this could be caused by the increased granulocytes, the source of transcobalamin I, in patients with CML. [22]

**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 with side chains of various lengths including farnesol, geranylgeraniol and geranylgeranisol toward leukemia cells *in vitro*. Menaquinone 3, 4, 5 and geranylgeranisol (at 10 microM) showed a potent apoptosis-inducing activity for all freshly isolated leukemia cells tested and for leukemia cell lines such as NB4, an acute promyelocytic leukemia (APL)-derived cell line and MDS92, a cell line derived from a patient with myelodysplastic syndrome. In contrast, Vitamin K1 (a natural derivative from fish or plants) showed no effect on any of the leukemia cells. The combination of menaquinone 5 plus all-trans retinoic acid (ATRA) resulted in enhanced induction of apoptosis in both freshly isolated APL cells and NB4 cells as compared to each reagent alone. These data suggest the possibility of using Vitamin K2 and its derivatives for the treatment of myelogenous leukemias, including APL. [23]

**Indirubin**

Indirubin, from *Indigofera tinctoria* or *Isatis tinctoria*, is the active ingredient of the Traditional Chinese Medicine recipe Dang gui Long hui Wan used against chronic myelocytic leukemia. [24] [25] [26] [27]

Indirubin has been found inhibit cyclin dependent kinases (CDKs) and glycogen synthase kinase-3. Aberrant expression of these proteins, are involved in the G1 phase of the cell cycle. [28] [29] [30] [31] [32] [33]

Studies of meisoindigo, an indirubin derivative, indicate that it strongly inhibits DNA biosynthesis in tumor cells and inhibits the assembly of microtubules. Experimental results on the mouse leukemia L1210 cell cycle showed that under the action of meisoindigo the S phase cells accumulated and the traverse of the cells in G2 + M phase to G1 phase may also be blocked to some extent. [34]

Mesoinigo has been shown to down-regulate c-myb, a gene that is required for progression in the S phase. [35]

Indirubin has also been shown to have an anti-inflammatory action by inhibiting the production of interferon-gamma, a well-known inflammatory cytokine. [36]

**Curcumin**

An article published in the *Journal of the American College of Nutrition* described a study of the effects of curcumins on different stages of development of cancer. Curcumin I and curcumin III, the yellow coloring phenolic compounds isolated from the spice turmeric, exhibit in vitro cytotoxicity against human chronic myeloid leukemia, in a dose dependent manner. [37] Several studies have sought to identify the mechanism of action of curcumin on leukemia.
Curcumin has been shown to inhibit apoptosis (programmed cell death) by inhibiting c-jun/AP-1 and bcl-2 (a key modulator of apoptosis). [38] [39] Interestingly, curcumin also promotes apoptosis through mitochondrial pathway involving caspase-8, BID cleavage, cytochrome c release, and caspase-3 activation. [40]

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. [41]

Conclusion

Several nutrients, botanicals, and their derivatives show promising in the treatment of chronic myelogenous leukemia. All-trans retinoic acid, vitamin A and vitamin D3 have shown benefit in patients with CML. In China, the flavenoid indirubin is used as a drug 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.

About the author

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References


