A Report on the Treatment of Chronic Myelocytic Leukemia (CML)\(^1\) complicated by Myelofibrosis with a Combination of Chinese and Western Medicines

by Simon Becker, Dipl. Ac. & C.H. (NCCAOM)

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The pluripotent stem cell, the hemocytoblast, is the original cell from which all other formed elements in the blood, such as the white and red blood cells as well as the platelets, develop. The hemocytoblast differentiates into two further stem cells: the myeloid stem cell and the lymphoid stem cell. The lymphoid stem cell goes on to differentiate into the B- and T-lymphocytes. The myeloid stem cell gives rise to all other white blood cells, platelets, and red blood cells. A leukemic transformation of the lymphoid line gives rise to either acute lymphoblastic leukemia (ALL) or chronic lymphocytic leuekmia (CLL). A leukemic transformation affecting primarily the myeloid line gives rise to either acute myeloid leukemia (AML) or chronic myelocytic leukemia (CML).

Acute leukemias (ALL and AML) generally present with high white blood cell counts and severe anemia. Their disease course is rapid and prognosis is poor. As outlined in some of my other articles on this subject\(^2\), both AML and ALL can be treated (more or less successfully depending on the patient’s condition) by a combination of Chinese and Western medicine.

Chronic lymphocytic leukemia (CLL) progresses more slowly than the acute forms. Its median survival period is about 10 years.\(^3\) Unlike in other types of leukemia, survival of CLL cannot be prolonged by Western medical treatment and it is important to realize that “treatment...may be associated with significant side effects. Overtreatment is more dangerous than undertreatment.”\(^4\) Because CLL is very rare in Japan and China, information on its Chinese medical treatment is difficult to find.

Chronic myelogenous leukemia (CML), the topic of this article, accounts for 20% of all leukemias in the West and is most common at the median age of 45 years, although it may occur at any age after 10 years. Often, CML is discovered by routine blood analysis or at a doctor’s visit prompted by the insidious onset of such symptoms as fatigue, weight loss or abdominal fullness. Generally, diagnosis of CML “is relatively easy because of the association of splenomegaly, leukocytosis with immature granulocytes and absolute increases in number of basophils and eosinophils...and the presence of the Ph chromosome\(^5\)\(^,\(^6\) Common clinical manifestations of CML are fatigue, weakness, anorexia, weight loss, fever, night sweats, and abdominal fullness. With progression of the disease, pallor (due to anemia) and bruising (due to thrombocytopenia) may also appear.

As the disease name points out, CML results from a malignant transformation of a pluripotent stem cell of the myeloid system with a primary overproduction of granulocytes. However, because the myeloid system gives rise to other formed elements, erythrocytes, megakaryocytes, and monocytes are also pathologically involved.\(^7\) This leads not only to elevated granulocyte levels, but also causes anemia with abnormally shaped erythrocytes and thrombocytopenia. Furthermore, the affected CML clone is unstable. With loss of differentiation and maturation of the granulocyte precursor, accumulation of blast cells\(^8\) leads to a so-called blast crisis. During the blast crisis, myeloblast tumors, called chloroma, can develop in other extramedullary sites such as the bones, CNS, lymph nodes and skin.

Generally, the bone marrow in CML patients is hypercellular and thus produces an excessive amount of white blood cells. Hence, the white blood cell count in CML patients is, in contrast to other leukemias,
almost always elevated. However, in 40% of patients, myelofibrosis will present at some point during the course of CML. Although the exact cause of myelofibrosis is unknown, a link seems to exist between its development and diseases such as chronic myelocytic leukemia or polycythemia vera as well as other neoplasms, infections, and exposure to toxins such as x- or gamma-radiation or benzene. It is characterized by bone marrow fibrosis, splenomegaly (which, in the case of myelofibrosis as a complication of CML, is usually already present) and a leukoerythroblastic anemia with, in advanced cases, teardrop erythrocytes. Bone marrow aspiration is often dry and bone marrow biopsy demonstrates fibrosis. To date, there is no therapy to reverse or control the underlying pathologic process.

Chronic myelocytic leukemia is treated primarily by chemotherapy. However, because chemotherapy does not affect the Philadelphia Chromosome or eradicate the source, the chemotherapeutic treatment goal is not cure but rather palliation. On the other hand, bone marrow transplant may be curative. In addition, splenectomy to remove the enlarge spleen may improve abdominal discomfort, improve thrombocytopenia, and reduce blood transfusion requirements. However, “there is no evidence that splenectomy plays a significant role during the chronic phase of disease control.” Much more important seems the control of the WBC count; it has been shown that keeping it below 50,000 leads to longer asymptomatic periods.

Median survival in CML patients is from 3 to 4 years after clinical onset. Most patients die during blast crisis or during an accelerated phase of the disease. If remission can be achieved after blast crisis, median survival can be prolonged from about 2 months in non-remission cases to 12 months in remission cases.

In China, Chinese medicinal therapy is regularly added to chemotherapeutic agents in the treatment of CML. The following functional translation of an article which first appeared in the May 1996 edition of the Shan Dong Zhong Yi Za Zhi (Shandong Journal of Chinese Medicine) reports about this combination of western and Chinese medicine. Besides presenting Chinese medical information, the article elaborates in detail about the biomedical diagnostic criteria. As a practitioner of Chinese medicine in the West, I find the biomedical details excessive and feel that the article could have elaborated more on the selected Chinese medicinals. A bit unfortunate from my Chinese medicine practitioner’s point of view is that the article elaborates about the biomedical data in more detail than on the Chinese medicine information. Nevertheless, I presents this article as information on CML is relatively rare to find in the modern Chinese medical literature and because it complements the still limited chapter in my A Handbook of Chinese Hematoloy very well by adding some clinically very useful information. I especially find the relatively complex base formulas for the three different patterns of CML interesting. Furthermore, with its less than stellar treatment outcome (9 out of the 12 patients eventually died), it is a very realistic example of the clinical outcome of the treatment of CML with a combination of Chinese and western medicine.

It is clear that in order to more conclusively determine if the addition of Chinese medicine to standard modern treatment protocols is of great or small value in the treatment of CML, more research, not only in China but also here in the West, is necessary. I hope that articles like the following provide the tools and stimulus for such research and thereby make the further collection of experiences possible.

[The Treatment of] 12 Cases of Chronic Myelocytic Leukemia (CML) complicated by Myelofibrosis

Cohort description

A total of 12 cases (9 male, 3 female) were treated. Out of the 12 cases, 6 were between 18-30 years old, 4 were between 31-45, and 2 were above 46.
Symptoms and Signs

All patients were diagnosed with CML complicated by myelofibrosis. Ten cases manifested with anemia, 4 cases with bleeding, 4 cases with fever, 8 cases with copious sweating, 6 cases with bursting fullness of the upper abdomen, 2 cases with joint pain, 3 cases with marked emaciation, 1 case with swelling of the lower limbs, 5 cases with lymphnode enlargement, 4 cases with sternal pressure pain, 7 cases with a swollen and enlarged liver, 11 cases with a swollen and enlarged spleen (in 4 cases the lower border was level with the umbilicus), and 1 case presented with ascites.

Laboratory Examinations

a) Peripheral blood: in all 12 cases, the red blood cell (RBC) count and hemoglobin level was decreased. In 2 cases, the hemoglobin was below 3g/dL, in another 2 cases it was between 3-6g/dL, in 5 cases between 6.1-9g/dL, and in 3 cases between 9.1-12g/dL. A peripheral blood smear showed the presence of an increased number of nucleated RBCs but no RBC shape abnormalities. As usual in CML, white blood cells were markedly increased; WBC count reached 10×10⁶/mL or higher with the highest number being 940×10⁶/mL. The peripheral blood smear also showed various developmental stages of juvenile blood cells; neutrophilic myelocytes as well as metamyelocytes were most common. Eight cases presented with basophilic granulocytosis. Once the condition became complicated by myelofibrosis, the increased WBC count markedly decreased; in 4 cases, it decreased to below normal levels, in 3 cases it decreased to between 4-10×10⁶/mL and in 5 cases to between 10-20×10⁶/mL. The peripheral blood still contained quite a few juvenile cells. Platelet count was below normal in only 1 case during the CML phase. However, after myelofibrosis transformation, it was below normal in 7 cases. No deformed platelets were seen in the peripheral blood. In one cases, fragments of megakaryocytic cells were present.

b) Bone marrow: During the CML phase, all 12 cases presented with typical CML marrow pathology. After transformation to myelofibrosis, 10 cases presented with dry aspiration. A bone marrow smear revealed active focal proliferation of the marrow with neutrophilic myelocyte proliferation and an increased myeloid : erythroid (M:E) ratio. Bone marrow biopsy revealed hypercellularity in 3 cases, collagen transformation in 5 cases and sclerosis in 4 cases.

c) Cytochemical staining: leukocyte alkaline phosphatase score was negative or low in 10 cases and normal in 2 cases.

Disease progression and change

Out of the 12 cases in this group, 2 cases suffering from an acute transformation of CML developed myelofibrosis after 150 days; 2 cases suffering from complicating myelofibrosis developed an acute leukemic transformation after 180-360 days; 3 cases diagnosed with CML simultaneously suffered from myelofibrosis, and 5 cases suffering from CML presented with myelofibrosis after 240 days to 5 years. Generally, after myelofibrosis had developed, the disease condition developed relatively quickly. Besides the 3 cases who experienced relieve, 9 cases died between 17 days and 1 year after complicating myelofibrosis had appeared. The causes of death were infections, bleeding or organ detriment. The natural disease course was 1-6 years and the median survival time 3.5 years.

Treatment

Chemotherapy: During the CML phase, patients were treated with intermittent chemotherapy; mostly, myleran (busulfan) and hydroxycarbamide were used. Myleran was administered as follows: 4mg twice
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daily for 7 days or 40mg once in the course of seven days for 14 days. Hydroxycarbamide was administered between 0.5 - 1g three times daily, maintaining 20mg/(kg\(\times\)d).

During acute transformations, the chemotherapeutic COAP and HOAP protocols\(^\text{17}\) were employed.

Chinese medicine: Treatment was based on pattern discrimination. If patients presented with qi and yin dual vacuity, the treatment principles were to boost qi and nourish yin, transform stasis and dissipate nodules. Commonly used medicinals were Radix Astragali Membranacei (Huang Qi), Radix Pseudostellariae Heterophyllae (Tai Zi Shen), Rhizoma Atractyloides Macrocephalae (Bai Zhu), Radix Angelicae Sinensis (Dang Gui), Tuber Bolbostemmatis (Tu Bei Mu)\(^\text{18}\), unprepared Radix Rehmanniae (Sheng Di), Tuber Ophiopogonis Japonici (Mai Men Dong), Conchae Ostreae (Mu Li), Radix Scrophulariae Ningpoensis (Xuan Shen), and Rhizoma Curcumae Zedoariae (E Zhu). If patients presented with qi and blood debility, the treatment principles were to supplement qi and nourish blood, transform stasis and disperse the disease. Commonly used medicinals were Radix Astragali Membranacei (Huang Qi), Radix Codonopsis Pilosulae (Dang Shen), Radix Angelicae Sinensis (Dang Gui), Rhizoma Atractyloides Macrocephalae (Bai Zhu), Radix Albae Paeoniae Lactiflorae (Bai Shao), cooked Radix Rehmanniae (Shu Di Huang), Sclerotium Poriae Cocos (Fu Ling), Fructus Lycii Chinensis (Gou Qi Zi), Conchae Ostreae (Mu Li), Tuber Bolbostemmatis (Tu Bei Mu), Herba Oldenlandiae Diffusae (Bai Hua She She Cao), Rhizoma Smilacis Glabrae (Tu Fu Ling)\(^\text{20}\), and Gelatinum Asini (E Jiao). If patients presented with accumulated and exuberant heat toxins, the treatment principles were to clear heat, resolve toxins, cool the blood and stop bleeding. Commonly used medicinals were unprepared Radix Rehmanniae (Sheng Di), powdered Cornu Rhinocerotis (Xi Jiao)\(^\text{21}\), Herba Oldenlandiae Diffusae (Bai Hua She She Cao), Radix Scrophulariae Ningpoensis (Xuan Shen), Herba Scutellariae Barbatae (Ban Zhi Lian), Radix Arnebiae seu Lithospermi (Zi Cao), Herba Cephalanoplos Segeti (Xiao Ji), Herba Agrimoniae Pilosae (Xian He Cao), Radix Isatidis seu Baphicacanthi (Ban Lan Gen), Herba Taraxaci Mongolici cum Radice (Pu Gong Ying), Fructus Forsythiae Suspensae (Lian Qiao), and Radix Panacis Quinquefolii (Xi Yang Shen). Medicinals were added to the above main medicinals depending on the individual patterns.

Treatment results

After the combined treatment with western and Chinese medicines, 3 cases (25%) experienced complete resolution. In 4 cases (33.3%), the disease resolved partly. In 5 cases (41.7%), the treatment did not lead to any improvement. Thus, the total amelioration rate was 58.3%.\(^\text{22}\)

Discussion

In Chinese medical theory, CML is often classified as vacuity taxation (xu lao). However, because an enlarged liver and spleen may be a prominent characteristic of this disease, it sometimes is also classified as accumulation (ji) disease. Because right qi is depleted and vacuous, evil toxins are contracted. The invading evil toxins cause qi to become stagnant, blood to become static and phlegm to bind internally. Thus lumps are formed and accumulation disease arises. Therefore, the treatment primarily focuses on supporting the right and securing the root. In addition, qi must be moved, blood quickened, phelgm transformed and lumps dissipated. If these treatment principles are adhered to and if treatment is administered based on pattern discrimination, the treatment results will be good.

Endnotes

1. Chronic myelogenic leukemia is also called chronic granulocytic leukemia. The myeloid stem cell gives rise to the granulocytic cells (neutro-, baso-, and eosinophils). Thus, if the leukemia affects the myeloid
series, it generally presents with a striking overproduction of granulocytes and is therefore also called granulocytic leukemia.


5. The CML clone is often, but not always, associated with the Philadelphia (Ph) chromosome. The chromosomal abnormality defined as a Ph chromosome is a translocation of an oncogene from chromosome 9 to chromosome 22. This leads to an altered expression of the gene and thus to the malignant transformation of the stem cell.


7. The lymphoid system may also be involved during blast crisis. This then gives rise to the appearance of pathological B- and T-lymphocytes in form of lymphoblast accumulations.

8. Blast cells are precursor cells to the “finished” cells circulating in the blood. In this case, the granulocytic blast cell, the myeloblast, does not differentiate and mature properly. The result is an accumulation of incompetent granulocytes: the blast crisis.

9. In the acute leukemias, the WBC count is elevated only in about 50%. In chronic lymphocytic leukemia, the chance for a normal or low WBC count lies by about 2%.

10. The spleen has the function to remove platelets and red blood cells from the blood. It accomplishes this by forcing the blood to flow through a net of very fine capillaries. In this capillary net, many platelets and RBC become entangled and are destroyed. In an enlarged spleen, this removal becomes excessive and leads to anemia and thrombocytopenia. Therefore, splenectomy of an enlarged spleen helps palliatively in the treatment of thrombocytopenia and anemia.


12. In my book (A Handbook of Chinese Hematology, Blue Poppy Press), I list two patterns for chronic leukemia: 1) essence debilitation & marrow vacuity with static blood and concretions and conglomeration and 2) qi and blood consumption and detriment with accumulation of exuberant evil toxins. All in all, they include the three patterns outlined in this article.


14. Red blood cells generally do not have a nucleus. Nucleated red blood cells is therefore a sign of some type of developmental abnormality of the RBC.

15. In patients suffering from chronic myelogenous leukemia, bone marrow is hypercellular on both aspirate and biopsy.
16. It is not entirely clear to me what is meant by “collagen formation” and “sclerosis.” It is assumed that both are types of marrow fibrosis. Furthermore, it is also not clearly stated in the translated article when in the disease course the bone marrow biopsy was performed. Taking in consideration the rest of the article, it is assumed that the biopsy was performed at the outset of treatment.

17. It is not clear to me, which exact chemotherapeutic protocols are referred to here. However, from the original article, it appears that they are standard chemotherapeutic therapies in the treatment of acute leukemia.

18. Tuber Bolbostemmatis (Tu Bei Mu) is the tuber of Bolbostemma paniculatum (Maxim.) Franquet. It is bitter and cool and has the function to dissipate nodulations and toxins and disperses swollen welling abscess (yong). Recommended daily dosage for internal administration in decoction form is 10-30g.

19. Herba Oldenlandiae Diffusae (Bai Hua She She Cao) is employed in two formulas in this study and is a commonly seen medicinal in the treatment of blood diseases. Bai Hua She She Cao is bitter, sweet and cold and enters the heart, liver and spleen. It clears heat, disinhibits dampness and resolves toxins. According to the Zhong Yao Da Ci Dian, Bai Hua She She Cao has an anti-cancer function; it especially seems to control and repress acute lymphocytic, monocytic and chronic granulocytic cancer cells (Zhong Yao Da Ci Dian [A Great Dictionary of Chinese Medicines], vol. 1, 1993, p. 754)

20. Radix Smilacis Glabrae (Tu Fu Ling) may seem like a strange medicinal in a qi and blood vacuity prescription. Tu Fu Ling is sweet, bland and level and enters the liver and stomach channels. It resolves toxins, eliminates dampness and disinhibits the joints. It is used to treat syphilis, strangury-turbidity, hypertonicity and pain of the sinews and bones, leg qi (jiao qi), clove sore (ding), swollen welling abscess (yong), and scrofula (luo li). Its application in the treatment of CML is related to its ability to treat luo li. Luo li refers to phlegm nodulation underneath the skin, most commonly underneath the armpit or on the sides of the neck. Medicinals treating scrofula, or luo li, do so because they dissipate phlegm nodulation. In CML, the swollen lymph nodes are a sign of phlegm nodulation. This is why Tu Fu Ling is employed in this base prescription.

21. Cornu Rhinocerotis is an endangered species on the CITES list (Convention on International Trade of Endangered Species) and trade is illegal. Substitution with Cornu Bubali (Shui Niu Jiao) is imperative. I believe that the original article refers to this medicinal simply as a representative and that in actuality Shui Niu Jiao, not Xi Jiao was used.

22. Unfortunately, the criteria for evaluating treatment effects are not given. I consider this to be a serious shortcoming which adds to the already not very concisely written report. However, because articles on CML and myelofibrosis are relatively scant in the modern Chinese medical literature and because the Chinese medical information provided in this article is clinically useful, I still decided to translate and publish it.