Prolonged Remission in Chronic Myeloid Leukemia
after One Course of Busulfan

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Prolonged remissions in chronic myeloid leukemia following treatment with busulfan have been reported by various authors.1-11 Although lengthy periods of latency of the disease following cytostatic treatment are not uncommon, the observation of a complete clinical and hematologic remission of nearly 7 years duration in a patient with chronic myeloid leukemia following a single course of busulfan seems sufficiently rare to justify its description.

Case Report

A. A. (Record No. 13521/56), a 42-year-old Israeli-born housewife, mother of two healthy children, was referred to the hematologic clinic of our hospital on November 9, 1956, because of persistent leukocytosis. In 1955 she had a 3-week period of fever, diagnosed by the family physician as viral pneumonia and treated with achromycin. A leukocyte count done at that time was 8400 per cu. mm. but a differential count had not been performed. Seven months prior to admission she underwent a tooth extraction without excessive bleeding. Shortly thereafter she began to complain of weakness, and blood examination revealed a white cell count of 25000 per cu. mm.

Physical examination on admission showed the patient in fair nutritional state and was unremarkable except for a firm and nontender spleen felt just below the costal margin. There was no lymphadenopathy. X-ray of the chest showed a normal mediastinal shadow. Blood examination revealed: hemoglobin 11.4 Gm./100 ml., RBC 3.35 × 10^8 per cu. mm., WBC 11,000 per cu. mm. with a differential count of 61 per cent polymorphonuclears, 7 per cent band forms, 3 per cent eosinophils, 1 per cent myelocytes, 23 per cent lymphocytes and 5 per cent monocytes. The platelet count was 175,000 per cu. mm.; the erythrocyte sedimentation rate was 24 mm. per hour. A sternal bone marrow puncture smear revealed marked hyperplasia of the white cell series with a few blasts. The red cell series was slightly hypolastic; megakaryocytes were scarce. Chronic myeloid leukemia was suspected and the patient was observed without treatment. During the next year (fig. 1) her hemoglobin varied between 11.5 and 13 Gm./100 ml., but the white cell count rose gradually, jumping in September 1957 to 270,000 per cu. mm. with a differential count of 36 per cent polymorphonuclears, 10 per cent band forms, 8 per cent metamyelocytes, 26 per cent myelocytes, 8 per cent premylelocytes, 2 per cent blasts and...
10 per cent lymphocytes. The hemoglobin was 12.3 Gm./100 ml.; the platelet count was 120,000 per cu. mm. A bone marrow smear revealed an essentially similar picture to the previous one, except that now extensive leukophagocytosis by macrophages was seen.

On September 10, 1957, treatment with busulfan, 4 mg. per day, was started. The hematologic course is shown in figure 1. On October 7, 1957, the spleen had become impalpable, the WBC had decreased to 54,000 per cu. mm., and the differential count was 60 per cent polymorphonuclears, 3 per cent band forms, 1 per cent eosinophils, 1 per cent basophils, 8 per cent monocytes, and 27 per cent lymphocytes. The dose of busulfan was gradually decreased and at the end of December 1957, about 3¾ months after beginning of the treatment and a total amount of 185 mg. busulfan, the drug was stopped. On December 31, 1957, the WBC was 5000 per cu. mm. with 58 per cent polymorphonuclears, 4 per cent band forms, 4 per cent eosinophils, 30 per cent lymphocytes, and 2 per cent monocytes. Since then the patient remained under careful observation of the hematology clinic, felt well, did her household work, and did not show any abnormal physical findings.

In January 1964 the patient had slight fever and muscle pains for a few days, diagnosed by her physician as a common cold. During this episode the WBC rose to 32,000 per cu. mm. with a shift to the left—14 per cent band forms and 60 per cent polymorphonuclear neutrophils. The blood count, however, returned rapidly to normal and a repeat examination on August 2, 1964, showed hemoglobin 12.9 Gm./100 ml., WBC 6600 per cu. mm. with 60 per cent polymorphonuclears, 3 per cent band forms, 2 per cent eosinophils, 30 per cent lymphocytes, 30 per cent monocytes. The only abnormal finding was a negative alkaline phosphatase reaction of the white cells in the peripheral blood smear. A serum vitamin B₁₂ determination performed at that time gave an elevated value of 1760 μg./ml.

On September 2, 1964, the patient had an upper respiratory infection with a temperature of 37.8 C. and general malaise. Physical examination was negative, but blood examination revealed WBC 40,000/cu. mm. with 24 per cent polymorphonuclears, 44 per cent band forms, 2 per cent eosinophils, 10 per cent metamyelocytes, 6 per cent myelocytes, 12 per cent lymphocytes, and 2 per cent monocytes. The platelet count was 140,000 per cu. mm., and hemoglobin 12 Gm./100 ml. Two weeks later she felt a sharp pain in the left upper abdomen; her temperature rose to 38.6 C.; and the WBC was 150,000/cu. mm. with a differential count similar to the previous one. White cell alkaline phosphatase in the peripheral blood smear gave a score of 12 per cent. (Normal value 30–80 per cent).* The temperature dropped after a few days without specific treatment, but the WBC remained at about 150,000 per cu. mm. Busulfan, 10 mg. per day, was started on September 16, 1964, and after a total amount of 110 mg. the WBC dropped on October 6, 1964, to 7100 per cu. mm. with a normal differential count. Serum vitamin B₁₂ on September 29, 1964, when the WBC was still elevated (85,000 per cu. mm.) was 2000 μg./ml. White cell alkaline phosphatase remained negative with a score of 17 per cent. On October 22, 1964, without further clinical or hematologic changes, the white cell alkaline phosphatase had become positive with a score of 53 per cent.

Chromosomal studies were performed on blood leukocytes three times. The method used was a modification of that of Hastings¹² (leukocyte cultures, using Phytohemagglutinin (PHA) as a mitogenic agent and colchicine for arresting mitosis in metaphase). The first culture, done in November 1963, was unsuccessful. The second one, in January 1964, gave good metaphases. The model number of chromosomes was 46; no Philadelphia chromosome was found in the metaphases scored, counted and analyzed.

In September 1964, at the peak leukocytosis (150,000/cu. mm.), an additional chromosome study (the third) was done. Blood cultures with and without PHA were per-

formed, and favorable metaphases were obtained. In the culture without PHA many dividing cells were present, but the cells showed some diminished readiness to spread satisfactorily and counting was somewhat difficult because of overcrowding of the chromosomes. In some of the metaphases without PHA, however, Ph1 chromosome was clearly identified. In the cultures with PHA, 22 cells were counted and 5 cells analyzed. The model number was 46 chromosomes; chromosome was present in three of the cells analyzed. One of them, with 47 chromosomes, contained the Ph1 (fig. 2). The additional chromosome, a submetacentric, resembled those of 6–12 × group.

DISCUSSION

The described case poses two interesting problems: diagnostic and therapeutic. First, the question may be asked whether the patient has leukemia or had a leukemoid reaction. Leukemoid reactions may accompany various abnormal conditions, such as infectious diseases, malignancy and hemolysis.13 In a series of 87 patients with leukemoid reaction reported by Seige and Jansen,14 the underlying disease was malignancy in 40 per cent, infectious disease in 40 per cent, and hemolytic anemia, kidney disease and diabetes in the remainder. The leukocytosis in leukemoid reactions can be considerable. Hinshaw et al.15 described a patient with metastasizing bronchial carcinoma with a white cell count of 144,000 per cu. mm. but without immature forms in the peripheral blood smear.

In our patient whose leukocyte count reached a value of 270,000 per cu. mm. with the appearance of large numbers of immature forms in the peripheral blood, including a few blasts, there was no evidence for a leukemoid reaction. She had no underlying disease conducive to such a reaction; the excessive leukocytosis and the enlargement of the spleen appeared in the absence of fever and of hemolysis and without a history of a previous infectious disease. In addition, her splenomegaly disappeared while under Myleran treatment, together with the abnormal blood picture.

Although unfortunately we could not perform an alkaline phosphatase staining on her white blood cells until, at the least, 4 years after the beginning of her disease, the fact that this histochemical reaction was negative on repeated
Fig. 2.—Leukocyte culture with PHA. Karyotype of the cell containing 47 chromosomes. The additional submetacentric resembling one of 6–12 X group. Note the minute Ph1 chromosome.

examinations during the last three years supports strongly the diagnosis of leukemia. In the light of observations reported in the literature, this diagnosis is not contradicted by the appearance of a positive leukocyte alkaline phosphatase reaction during the patient's recent remission. Additional evidence for leukemia was the finding of an elevated serum B12 value on two occasions, once while the patient had an elevated white cell count and once while being in remission. The chromosomal studies confirm the diagnosis of leukemia in this patient and reflect the condition in the different stages of her illness: re-
mission—without any abnormality in her chromosome complement; and the stage of relapse—when the Ph1 was found in the metaphases of the leukocyte cultures with and without phytohemagglutinin. One would expect a high percentage of the abnormal chromosome in bone marrow aspirates even during remission. Unfortunately, however, further bone marrow aspiration was refused by the patient.

The prolonged remission in the present case is the more remarkable since it followed a single and relatively short course of busulfan treatment. According to Shilling et al., the best therapeutic results in chronic myeloid leukemia are obtained when treatment is started early in the course of the disease. Some investigators are of the opinion that in order to obtain remission the leukocyte count should be decreased to 5000–10000 per cu. mm., or even pancytopenia should be attained. The prolonged remissions obtained with busulfan in most of the described cases required continuous or repeated treatment. Similarly, in several cases of chronic myeloid leukemia which were under our observation and in whom prolonged remission was obtained by busulfan, the drug had to be given continuously, and each time treatment was stopped, relatively soon a rise in the leukocyte count and appearance of young white cells in the peripheral blood could be noted. One such patient with chronic myeloid leukemia has been treated by us for 9 years until demise.

We did not find in the literature a case of chronic or subacute myeloid leukemia with such a prolonged remission after discontinuation of treatment. Galton and Till achieved a remission of 4 years in one patient after a single course of busulfan treatment, and Haut et al. described a remission obtained by busulfan treatment by 4 years, Shilling of 2½ years, and Wilkinson of 23 months, but the mode of busulfan administration in these cases was not clearly presented.

A few reports have appeared describing in chronic myeloid leukemia spontaneous remissions and even cure, but doubt has been expressed as to the accuracy of the diagnosis in these cases. Forkner described a patient with chronic myeloid leukemia with a course of 11 years without treatment, with leukocytosis up to 30,000 per cu. mm. and a considerable number of myelocytes and myeloblasts in the peripheral blood. The criticism might therefore be made that in the present case we are dealing with a spontaneous remission. However, the course of the disease prior to treatment—i.e., gradual increase of the leukocyte count to excessive values and increase in size of the spleen—and the improvement in the patient’s condition coinciding with the busulfan treatment makes a spontaneous remission highly improbable.

Of great interest is the repeated negative alkaline phosphatase reaction of the white blood cells in our patient in the absence of any clinical or hematologic evidence of leukemia. Similarly, Kenny and Moloney did not observe a change in white cell alkaline phosphatase with improvement in their patient’s condition. On the other hand, according to Hayhoe, in patients with chronic myeloid leukemia the alkaline phosphatase of the white blood cells returns to the lower border of normal in remission and in rare cases even to completely normal. According to Xefteris et al., who confirmed Hayhoe’s observations, the return of the alkaline phosphatase reaction to normal in chronic myeloid
leukemia points to a better prognosis, such patients having a longer life span than those in which the alkaline phosphatase did not rise. It is speculative whether the recently found positive white cell alkaline phosphatase reaction in our patient points to her being in a more complete hematological remission as compared to the previous one.

**Summary**

A patient with chronic myeloid leukemia in whom a clinical and hematologic remission of nearly 7 years duration occurred after a single short course of busulfan is described. The only abnormal finding during the remission was a negative alkaline phosphatase reaction in her leukocytes. Chromosomal studies prior to relapse revealed a normal karyotype, and no Philadelphia chromosome was found. During relapse renewed chromosomal study revealed Philadelphia chromosome in metaphases of peripheral blood leukocytes.

**Summary in Interlingua**

Es describite le caso de un paciente con chronic leimcemia myeloide in qui un remission clinic e hematologic de un duration de quasi 7 annos occurreva post un sol breve curso de busulfan. Le sol constatation anormal durante le periodo del remission esseva un negative reaction de phosphatase alcalin in su leucocytos. Studios chromosomal ante le recidiva revelava un caryotypo normal, e nulle chromosoma Philadelphia esseva trovate. Durante le recideva, un repetition del studios chromosomal revelava le presentia de chromosomas Philadelphia in metaphases de leucocytos del sanguine peripheric.

**References**

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