Cytotoxic Chemotherapy for Cancer in Felty's Syndrome: Role of Lithium Carbonate

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A 61-yr-old white man with Felty's syndrome, who had previously undergone splenectomy, presented for cytotoxic chemotherapy. Random granulocyte counts remained low, prohibiting the initiation of such treatment. A trial of lithium carbonate was instituted, resulting in prompt elevation of granulocyte counts into the normal range. Cytotoxic chemotherapy was then administered, and fluctuations of neutrophil counts similar to those of hematologically normal individuals were observed.

Increased numbers of circulating neutrophils have been observed in psychiatric patients receiving lithium carbonate for manic-depressive disorders. This salutary effect on granulocyte number has been applied in several neutropenic disorders, including Felty's syndrome, characterized by rheumatoid arthritis, splenomegaly, and neutropenia, and in the attenuation of myelosuppression from cytotoxic chemotherapy. In the patient presented here, lithium carbonate-enhanced granulopoiesis allowed the initiation of chemotherapy in a man with Felty's syndrome whose pretreatment neutrophil counts would have precluded cytotoxic chemotherapy. The cyclic granulocyte fluctuations observed were similar to those expected in hematologically normal subjects.

CASE REPORT

A 61-yr-old white office worker with the diagnosis of Felty's syndrome presented for consideration of adjuvant chemotherapy in March 1979 after total gastric resection.

In 1964, the patient was noted to have symmetrical polyarthritis, and in May 1977, the diagnosis of Felty's syndrome was established. Evaluation included a rheumatoid factor of 1:1280, sedimentation rate of 84 mm/hr, neutrophil count of 0.065 x 10^9/liter, hematocrit of 35 vol%, and a normal platelet count. Splenomegaly was present on physical examination, and a bone marrow aspiration revealed a hypercellular marrow with granulocytic hyperplasia. When uninfected, all random peripheral blood granulocyte counts were low; "cycling" was never seen. The patient developed Pseudomonas sepsicemia, and an emergency splenectomy was performed at another institution in August 1977. A transient increase of the white blood cell count to 6.0 x 10^9/liter was then obtained, reportedly with a normal differential count. In 1979, vague abdominal pain and fever resulted in an exploratory laparotomy that revealed a 3-cm gastric ulcer. Histologic examination confirmed a gastric adenocarcinoma, and a total gastrectomy and jejunoileal anastomosis were performed. Tumor invasion was demonstrated through the serosa; however, regional lymph nodes were free of metastatic involvement. The preoperative neutrophil count was 1.8 x 10^9/liter.

The patient was to receive cytotoxic chemotherapy in accordance with a multiinstitutional randomized adjuvant chemotherapy study for high-risk gastric cancer patients and was referred to Rush-Presbyterian-St. Luke's Medical Center for administration of this treatment. Several granulocyte counts were then found to be approximately 0.7 x 10^9/liter.

Because of the patient's persistent desire to proceed with therapy, a trial of lithium carbonate was instituted in March 1979, with an increase of the neutrophil count to 2.5 x 10^9/liter over the subsequent 2 wk. Chemotherapy was then administered according to the schedule and dosages depicted in Fig. 1. The patient tolerated the chemotherapy well with dose modifications (treatments B-D, see Fig. 1) subsequent to the neutropenia observed after treatment A. Because of a rising carcinoembryonic antigen (CEA) titer, an exploratory laparotomy was performed on day 238, which failed to demonstrate recurrent or persistent disease. Lithium carbonate was discontinued 2 days prior to the surgery. A culture-negative febrile illness resulted in an increased granulocyte count. After the febrile episode (and the discontinuation of lithium), the patient returned to his persistent neutropenic state (see Fig. 1).

DISCUSSION

Felty's syndrome is characterized by splenomegaly, neutropenia, and rheumatoid arthritis. The clinical course is frequently marked by repeated infections, often life-threatening. A definite correlation between the severity of neutropenia and frequency of infection, as observed in leukemia, has not been delineated in Felty's syndrome. Nevertheless, the major clinical application of lithium carbonate in Felty's syndrome has been aimed at increasing the granulocyte count to avert infections. This report indicates an additional role of the drug in these patients. Lithium carbonate may increase the total neutrophil count to allow the initiation of cytotoxic chemotherapy.

In the present case, an absolute neutrophil count of 0.7 x 10^9/liter at the start of chemotherapy would have precluded the use of cytotoxic regimens effective in gastric carcinoma. However, with lithium carbonate, an increase of the neutrophil count to 2.5 x 10^9/liter allowed effective delivery of drugs without serious or unusual myelosuppression. Serum lithium levels were monitored weekly and were maintained in the therapeutic range for psychiatric patients.
Fig. 1. Graphic illustration of the course of the patient described in this article. Each arrow indicates the day on which the particular chemotherapy course was initiated.
During therapy with lithium, the patient experienced a tolerable fine tremor that abated despite continuation of therapy. Interestingly, after discontinuation of lithium carbonate, a febrile episode was observed.

The cyclic nature of the granulocyte count observed in this case is similar to that noted in hematologically normal individuals receiving the same chemotherapeutic regimen. The nadir of the granulocyte count after 5-fluorouracil occurs approximately 10 days after administration, whereas methyl-CCNU causes a delayed and prolonged nadir occurring approximately 28 days after receiving the drug. Myelosuppression on days 21–35, as experienced by our patient, has also been noted in some of our hematologically normal patients receiving the same drugs. In addition, after this period of myelosuppression, our patient’s neutrophil count rose abruptly to his new baseline level achieved after initiating lithium.

Splenectomy in Felty’s syndrome may initially give beneficial results. Although granulocyte counts in the normal range may be achieved initially, they may not be sustained. The lack of uniform response to splenectomy suggests that hypersplenism alone is not the cause of the neutropenia. Of the 18 reported patients given treatment with lithium carbonate for Felty’s syndrome, none has been reported to have undergone previous splenectomy. Our patient has had a prior splenectomy that failed to alter his granulocyte count permanently.

Decreased urinary and serum granulocyte colony-stimulating activity (CSA) has been documented in splenectomy suggests that hypersplenism alone is not the cause of the neutropenia. Of the 18 reported patients given treatment with lithium carbonate for Felty’s syndrome, none has been reported to have undergone previous splenectomy. Our patient has had a prior splenectomy that failed to alter his granulocyte count permanently.

Decreased urinary and serum granulocyte colony-stimulating activity (CSA) has been documented in Felty’s syndrome. Although the nature of this defect is not well elucidated, low levels of CSA are presumably secondary to a defect of the monocyte-macrophage system responsible for CSA production. An increase of the total neutrophil mass rather than a shift among granulocyte pools occurs with lithium carbonate therapy. The drug has been shown to increase the production of CSA both in vivo and in vitro. By stimulating de novo production of CSA and causing expansion of the bone marrow granulocyte-committed stem cell compartment, lithium carbonate produces a concomitant elevation of peripheral granulocytes and serum CSA, as described in Felty’s syndrome. This observation suggests that the drug’s activity is augmentation of inherently low CSA in this disorder. The clinical efficacy of lithium may be greatest in neutropenic disorders with reduced CSA production. Although there exist data suggesting impaired bactericidal activity of granulocytes exposed to lithium, most studies have demonstrated that several aspects of granulocyte function remain intact.

This article identifies an additional clinical application of lithium carbonate. Its use allowed the initiation of cytotoxic chemotherapy in a patient whose pretreatment neutrophil count would have precluded such therapy. The cyclic granulocyte counts expected from this chemotherapy in hematologically normal subjects were observed. In the patient described, we have combined two previously reported hematologic applications of lithium carbonate: its use in patients receiving myelosuppressive chemotherapy, and its application in Felty’s syndrome.

REFERENCES

19. Pandy GN, Davis TJ: Biology of the lithium ion, in Rossof


Cytotoxic chemotherapy for cancer in Felty's syndrome: role of lithium carbonate

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