Therapy of Essential Thrombocythemia With Thiotepa and Chlorambucil

By Delwyn C. Case, Jr.

Twenty-seven patients with essential thrombocythemia were treated with combination chemotherapy consisting of weekly intravenous thiotepa (until the platelet count fell below $1,000 \times 10^3$/cu mm) and daily chlorambucil (until a sustained remission, platelet count less than $400 \times 10^3$/cu mm). All patients responded promptly, platelet counts fell below $1,000 \times 10^3$/cu mm by 1–3 wk, and were less than $400 \times 10^3$/cu mm by 2–6 wk. Remission of thrombocythemia was accompanied by an improvement of the patients’ symptoms and resolution of the splenomegaly that was present in 21 of the 27 patients. However, daily chlorambucil for more than 1 yr was required to produce a sustained remission in the majority of patients. Nine of 21 patients whose initial treatment was discontinued have required retreatment. To date, 3 patients have expired; 1 patient developed acute leukemia at 36 mo.

In the absence of a disease-specific marker, essential thrombocythemia has been defined as a myeloproliferative disorder of clonal origin characterized by a platelet count of greater than $1,000 \times 10^3$/cu mm in the absence of an increased red blood cell mass, a positive Philadelphia chromosome, myeloid metaplasia, or iron deficiency. While patients may tolerate strikingly high platelet counts for years without clinical sequelae, several reports suggest that such patients are at an increased risk for hemorrhagic and thrombotic complications. In fact, prior to the advent of chemotherapy, survival was said to be less than 3 yr, with death usually from hemorrhage or thrombosis of a major vessel.

Treatment appears justified in patients who are clearly symptomatic, with platelet counts greater than $1,000 \times 10^3$/cu mm. Prompt remissions have been achieved with alkylating agents, particularly P32 and busulfan. The present study describes the experience with a protocol utilizing thiotepa and chlorambucil. Inclusion of patients in this study was based on criteria also utilized by the Polycythemia Vera Study Group. This combination of thiotepa and chlorambucil produces a rapid response in the platelet count and symptomatic improvement. The initial morbidity is negligible, although daily chlorambucil therapy is often required for more than 1 yr to achieve a sustained remission.

MATERIALS AND METHODS

Previously untreated patients were considered eligible for study if they met the following criteria: (A) a platelet count in excess of $1,000 \times 10^3$/cu mm not attributable to other identifiable causes; (B) a hypercellular bone marrow with increased numbers of megakaryocytes; (C) absence of a Philadelphia chromosome; (D) normal or high leukocyte alkaline phosphatase score; and (E) a normal red cell mass or a hemoglobin less than 13 g/dl. Patients were excluded if they demonstrated significant marrow fibrosis on biopsy or iron deficiency with associated thrombocytosis.

Thiotepa was administered intravenously at a dose of 25 mg/sq m at weekly intervals until the platelet count fell below $1,000 \times 10^3$/cu mm. Chlorambucil was begun concurrently, with a daily dose of 6 mg/sq m. Patients were followed weekly until the platelet count was less than $400 \times 10^3$/cu mm, and then at monthly intervals. The dose of chlorambucil was tapered by 2–4 mg/day each month as long as the platelet count was below $400 \times 10^3$/cu mm and the white blood cell count greater than $4 \times 10^3$/cu mm. Chlorambucil was discontinued once the daily dose fell below 2 mg. Afterwards, patients were followed up every 3 mo. Once a sustained remission was achieved, a repeat bone marrow examination was performed.

If the platelet count could not be maintained below $400 \times 10^3$/cu mm with tapering doses of chlorambucil, the drug was continued at the lowest possible dose and tapering attempted again within 3–6 mo. Patients relapsing after thiotepa/chlorambucil were retreated with the same protocol in an attempt to induce a second remission.

RESULTS

Between 1976 and 1982, 27 patients with essential thrombocythemia were enrolled in the study. The median age of the patients was 67 yr (range 43–89 yr). Seventy-four percent were women. Eighty-five percent of the patients were symptomatic, complaining of one or more of the following: significant malaise and/or weakness (49%), weight loss of greater than 10 lb (41%), peripheral vascular insufficiency or symptoms or signs of arterial thromboembolism (26%), and abnormal bleeding (18%). Of the 7 patients with vascular insufficiency or arterial thromboembolic symptoms, 4 had peripheral arterial insufficiency with distal cyanosis and 3 had cerebral symptoms (2 with transient ischemic attacks and 1 with a completed ‘stroke’). Of the 5 patients with bleeding, 2 patients had easy bruising, 1 patient had extensive subcutaneous bleeding following an intramuscular injection, and 2 patients had significant generalized gastrointestinal...
tinal hemorrhage. Seventy-eight percent of patients had splenomegaly and 11% had hepatomegaly. The distribution of blood counts is shown in Fig. 1. The median platelet count was $1,700 \times 10^3$/cu mm and the majority of patients also demonstrated mild to moderate leukocytosis and/or anemia.

In accordance with the eligibility criteria, all patients showed hypercellular marrows with increased numbers of dysplastic megakaryocytes, a moderate increase in reticulin without frank myelofibrosis, and normal iron stores (25 of 27 patients). The two patients with absent iron stores did not show a significant fall in platelet count with oral iron therapy.

All patients had a prompt response to therapy, with the platelet count falling to below $1,000 \times 10^3$/cu mm within 3 wk and below $400 \times 10^3$/cu mm by 6 wk. The median nadir for the white blood cell count during initial therapy was $3.5 \times 10^3$/cu mm (range $1.8-7.6 \times 10^3$/cu mm). The mean nadir for the platelet count was $180 \times 10^3$/cu mm (range $78-280 \times 10^3$/cu mm). All patients had significant improvement in constitutional symptoms, organomegaly, and anemia. The 6 patients with symptoms of peripheral and cerebrovascular insufficiency demonstrated improvement with reduction in their platelet counts. Distal cyanosis resolved and circulation appeared improved. One of these patients presented with impaired healing from an amputation site, the surgery for which was required for peripheral vascular insufficiency; healing occurred only after the platelet count was restored to normal. In the patients with cerebral vascular symptoms, transient ischemic attacks did not recur after treatment was initiated. Splenomegaly resolved in the 21 patients presenting with splenic enlargement. The improvement in the hematocrit with thiotepa/chlorambucil therapy is depicted in Fig. 2. Of the five patients who presented with bleeding manifestations, two patients with generalized bruising showed no improvement with therapy. Bleeding times have remained prolonged. The one patient who had had an extensive subcutaneous bleeding following intramuscular injection recovered without incident. Bleeding ceased and did not recur in the two patients with gastrointestinal hemorrhage. Both patients with gastrointestinal bleeding were managed at outlying hospitals without pheresis availability. Bleeding times were grossly abnormal in these patients. Acutely, transfusions of normal platelets were given to each patient. Bleeding diminished after the transfusions and resolved as the platelet counts fell toward normal with chemotherapy.

Although the initial reduction of the platelet count was accomplished quite easily, there was considerable variability in the duration and dose of chlorambucil
required to maintain the platelet count below 400 \times 10^3/cu mm. It was possible to discontinue chlorambucil therapy in 21 of 27 patients after 5–36 mo (median 14 mo) of therapy. However, 9 of these patients have required retreatment after a median of 24 mo of unmaintained remission (Fig. 3). Retreatment has consisted of 6–18+ mo of daily chlorambucil therapy in order to sustain platelet counts less than 400 \times 10^3/cu mm.

Survival from initiation of therapy is also shown in Fig. 3. Overall survival is projected to be 85% at 5 yr. Three patients have expired to date—1 from a myocardial infarction at 15 mo, 1 from lung cancer at 36 mo, and 1 patient from acute myelomonocytic leukemia after 36 mo. The patient developing acute myelomonocytic leukemia was originally treated with 2 doses of thiotepa and 2 8-mo courses of daily chlorambucil, at an average dose of 4 mg/day.

Bone marrow examinations have been performed in 15 patients following discontinuation of chlorambucil therapy. Thirteen marrows were considered normal, while 2 marrows showed persistence of dysplastic megakaryocytes.

**DISCUSSION**

In the past, it has been debated whether patients with essential thrombocythemia should be treated on the basis of an increased risk of hemorrhagic or thrombotic complications, since thrombocytosis does not appear necessarily to correlate with a consistent dysfunction of platelets or increased risk of thromboembolic disease. A minority of patients in this series presented with bleeding or thromboembolic disease. This low incidence of thrombohemorrhagic phenomena may be unexpected by reviewing the classical essential thrombocythemia literature, but it is very similar to findings of the latest Polycythemia Vera Study Group report concerning the symptoms and laboratory features of patients with essential thrombocythemia. The constitutional symptoms and complicating anemia in this series were significant enough to prompt evaluation; one-half of the patients were hospitalized at the time of diagnosis for disease-related symptoms or signs. The resolution of the patients’ symptoms, organomegaly, and anemia appears to validate the appropriateness of chemotherapy in such patients.

The present results compare favorably to the randomized radioactive phosphorus/melphalan trial previously reported. The thiotepa/chlorambucil combination may even offer an advantage over drugs such as mechlorethamine, radioactive phosphorus, and busulfan in terms of morbidity and marrow toxicity during therapy. In the present study, platelet counts were readily maintained in the range of 150–400 \times 10^3/cu mm with relative ease without apparent marrow toxicity, even after 36 mo of daily chlorambucil. However, as with other regimens, the thiotepa/chlorambucil protocol does not produce sustained, unmaintained remissions. While drugs could be discontinued in 21 of 27 patients, 9 of these patients have already demonstrated a relapse within 2 yr. Therefore, sustained alkylating agent therapy would appear to be required if platelet counts are to be maintained below 400 \times 10^3/cu mm.

This finding raises the issue of drug-induced second malignancies. As with the previous studies of polycythemia vera, prolonged chlorambucil therapy may be associated with an increased incidence of acute myelocytic leukemia. In this series, after a median follow-up of 36 mo, one patient has developed acute leukemia. Moreover, essential thrombocythemia, which appears to be a myeloproliferative disorder of clonal origin, may be at increased risk of stem cell neoplastic transformation.

In conclusion, the combination of thiotepa and chlorambucil provides a reliable regimen for the rapid control of high platelet counts in patients with essential thrombocythemia. It results in a marked improvement in constitutional symptoms, a disappearance of splenomegaly, and a marked reduction in megakaryocyte mass with improvement in the patient’s anemia. Acute marrow toxicity is not a problem, although long-term therapy may produce leukemic transformation.

**REFERENCES**


Therapy of essential thrombocythemia with thiotepa and chlorambucil

DC Jr Case