Essential thrombocythemia (ET) is a clonal disorder of the myeloid stem cell characterized in the bone marrow by pathological expansion of the megakaryocytic elements, with a persistent increase in the platelet count. This chronic myeloproliferative disorder (CMD) does not present the Philadelphia chromosome or an increased red cell mass. The clinical course of patients affected by ET shows long intervals without any symptoms, but thromboembolic or hemorrhagic events can frequently occur.

Therapy with alkylating agents and radioactive phosphorous has been more or less abandoned since it may increase the frequency of terminal blast transformation,\(^1\) which can nevertheless occur in the natural course of the illness.\(^2\)

Hydroxyurea (HU), a non-alkylating agent, is usually considered the preferred treatment in patients with ET. Although it is generally safe and easy to use, some authors have reported cases of blast transformation during HU treatment, and there are also theoretical reasons for believing that this could occur (reviewed in ref. #3).

Pipobroman is also considered to have low leukemogenic potential and for this reason various European clinicians have tended to prefer it\(^4,6\) (and others reviewed in ref. #6) in polycythemia vera (PV) and ET, with good results on myeloid bone marrow proliferation.

Pipobroman, marketed under the commercial name of Vercyte, is a bromide derivative of piperazine, 1-4 bis (3-bromopropionyl)piperazine. It is a neutral amide derivative of nitrogen mustard (\(\text{NH}_2\)) containing part of the piperazine ring. This formula and the drug’s mechanism of action are close to those of the alkylating agents, but it also appears to act as a metabolic competitor for pyrimidine nucleotides. Above all, pipobroman inhibits the activity of DNA and RNA polymerases.\(^4\)

Case report

We describe an ET patient presenting myelodysplastic transformation (RAEB-t) after therapy with pipobroman at variable dosages.

---

Correspondence: Stefano Sacchi, M.D., Dipartimento di Scienze Mediche, Oncologiche e Radiologiche, Sezione di Medicina Interna, Università di Modena; \(^*\)Divisione di Ematologia, Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia, Italy

Received August 16, 1995; accepted November 27, 1995.
A 53-year-old man was first seen in February 1985. He presented paresthesias and acrocyanosis dating back some months. ET was diagnosed according to Polycythemia Vera Study Group criteria. The peripheral blood showed: Hb 15.1 g/dL, Hct 44.9%, WBC 12.1×10⁹/L and a platelet count of 984×10⁹/L. The leukocyte differential count was: neutrophils 80%, lymphocytes 14%, monocytes 5%, eosinophils 1%. Bone marrow aspiration and biopsy samples demonstrated an abnormal proliferation of the megakaryocytic elements in the absence of significant fibrosis. Echography showed a normal sized spleen. Cytogenetic study documented the absence of the Philadelphia chromosome.

The patient was first treated with pipobroman at a standard dose of 75 mg/day for 15 days, followed by 50 mg/day until remission. Therapy was stopped after one month in the light of good results: Hb 13.9 g/dL, WBC 4.2×10⁹/L and platelet count 279×10⁹/L. From April 1985 to November 1986, the patient remained in complete hematological and clinical remission, with a platelet count well below 400×10⁹/L without any therapy. In December, the platelet count increased to 553×10⁹/L and remained at this value until June 1987 when pipobroman was restarted at a dose of 25 mg/day for ten days each month because of some nasal bleeding. Arterial blood pressure was normal.

In November 1987, the dosage was reduced to 25 mg/day for seven days a month, given the reduced platelet count. In August 1988, patient became reluctant to continue clinical check-ups and decided to give all therapy to himself. As far as we can establish, he took pipobroman at a dose of 25 mg/day for 10 days each month because of some nasal bleeding. Arterial blood pressure was normal.

In January 1995, he was hospitalized in our Department for increasing fatigue, headache, dyspnea and splenic pain. The peripheral blood showed: Hb 8.6 g/dL, Hct 24.2%, WBC 5.5×10⁹/L, platelets 20×10⁹/L. The leukocyte differential count was: neutrophils 77%, lymphocytes 16%, metamyelocytes 1%, myelocytes 1% and blasts 5%. Bone marrow aspiration and biopsy samples demonstrated a myelodysplastic syndrome defined as RAEB-t according to the FAB classification. Echography showed an enlarged spleen (17 cm). A cytogenetic study of bone marrow cells indicated a chromosomal abnormality: 46, XY, del(11q)(q13-q23).

In February 1995, the patient began RBC transfusion and low-dose cytosine arabinoside; in July 1995, he is still alive, although he has not reached a partial or complete hematological remission.

**Discussion**

We describe here an ET patient presenting myelodysplastic transformation (RAEB-t) after therapy with pipobroman as the only chemotherapeutic agent. A cytogenetic study showed del(11q)(q13-q23). Rearrangements of 11q23 have increasingly been recognized in secondary MDS/AL and recently were reported in patients who had received Topo-II-targeting drugs, often in combination with alkylating agents, for their primary neoplasm.7-8

Najman4 described 3 cases of acute myeloid leukemia (AML) in PV patients treated with radioactive phosphorous before pipobroman. Chistolini9 carried out a retrospective study on the clinical course of 100 patients affected by ET, observing two cases of blastic transformation in 72 patients receiving pipobroman therapy. Boivin6 described 9 cases of blastic transformation in PV patients treated with pipobroman alone, 5 in the course of the first 10 years and 4 after 10 to 20 years of therapy. Spadea in a retrospective analysis of 204 PV patients treated with pipobroman found the presence of AML in 5% of patients after a median treatment time of 85 months (range 13-188).10

We believe that these observations indicate that pipobroman treatment may be associated with an increased incidence of terminal blast transformation. Consequently, clinicians should use pipobroman like any other chemotherapeutic drug, since it appears to be very similar to alkylating agents.

Recently, Cortelazzo showed that HU is effective in preventing thrombosis in high-risk
Secondary MDS in essential thrombocythemia patient

patients with ET, but the same author conclud-
ed that particular care should be exercised in
prescribing this drug to young patients because
the risk of secondary leukemia is not known.

To date, there is no generally accepted treat-
ment for ET able to reduce the risk of throm-
boembolism and/or hemorrhagic events and
avoid any increase in the frequency of sec-
ondary myelofibrosis and terminal blast trans-
formation.

Symptomatic patients are always treated, but
it is extremely difficult to decide whether or not
to treat asymptomatic cases. Thus, therapy
ranges from none to the use of myelosuppres-
sive drugs. The efficacy of α-IFN in ET patients
has been reported by several authors (reviewed
in ref. #3); this drug reduces the platelet count
rapidly, controls symptoms related to thrombo-
cytosis and might be able to suppress abnormal
clones in PV and ET patients. Since chronic α-
IFN treatment is very expensive and may pro-
duce severe side effects, this treatment is not
generally accepted. Anti-aggregating drugs may
be inadvisable because of the risk of hemor-
rhagic events. Anagrelide is not commercialy
available and can rarely be obtained for com-
passionate use.

We therefore conclude that the problem of
identifying the best form of ET treatment is far
from being resolved.

References

2. Geller SA, Shapiro E. Acute leukemia as a natural sequel to
3. Sacchi S. The role of α-interferon in essential thrombo-
cytaphaemia, polycythaemia vera and myelofibrosis with
myeloid metaplasia (MMM): a concise update. Leuk Lympho-
Pipobroman therapy of polycythemia vera. Blood 1982; 59:
890-4.
5. Brusamolino E, Salvaneschi L, Canevari A, Bernasconi C.
Efficacy trial of pipobroman in polycythemia vera and incid-
6. Boivin P. Indications, procedure and results for treatment of
polycythemia vera by bleeding, pipobroman and hydroxy-
7. Levine EG, Bloomfield CD. Leukemias and myelodysplastic
syndromes secondary to drug, radiation, and environmental
8. Gill Super HJ, McCabe NR, Thirman MJ, et al. Rearrange-
ments of the MLL gene in therapy-related acute myeloid
leukemia in patients previously treated with agents targeting
thrombocythemia: a retrospective study on the clinical course
polycythemia vera patients: a retrospective analysis. Blood
1994; 84 (suppl 1): 222a.
patients with essential thrombocythemia and a high risk of
Immune-mediated and unusual complications during alpha-
interferon therapy in chronic myelogenous leukemia. J Clin