Uracil Mustard in the Treatment of Thrombocythemia

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THROMBOCYTHEMIA with platelet counts of over 1,000,000 per cu. mm. may occur in a number of myeloproliferative disorders and may be associated with both thrombosis and hemorrhage. Either busulphan or radioactive phosphorus is generally used to reduce high platelet counts when they occur in these disorders. However, neither of these means of treatment is entirely satisfactory. A prolonged course of busulphan may be required to lower the platelet count, and not infrequently either drug will fail to produce a remission. At present there is also uncertainty as to the leukemogenic properties of radioactive phosphorus.

This report is to draw attention to the value of uracil mustard in the treatment of thrombocythemia. It describes its use in five patients. Three suffered from polycythemia vera with thrombocythemia and one had responded poorly to treatment with radioactive phosphorus. In the fourth patient thrombocythemia occurred during the course of chronic myeloid leukemia despite busulphan therapy and the fifth suffered from hemorrhagic thrombocythemia. The results obtained with uracil mustard suggest that it has advantages over other agents presently used to reduce high platelet counts in these conditions.

CASE REPORTS

Polycythemia Vera with Thrombocythemia

Case 1. The patient, a 59-year-old woman, was admitted to hospital because of a spontaneous hemorrhage which formed a large subcutaneous hematoma extending over most of the posterior aspect of the right thigh. Three months previously a smaller hemorrhage had occurred in her other thigh. Apart from bruising easily for the past six months, there had been no other symptoms of abnormal bleeding and she felt otherwise well. On examination it was noted that the spleen was palpable one inch below the costal margin on inspiration. Laboratory investigations revealed: Hemoglobin, 11.5 Gm./100 ml.; hematocrit, 39 per cent; platelets, 2,320,000 cu. mm. and WBC, 16,000 cu. mm. with neutrophils 92 per cent, basophils two per cent, lymphocytes five per cent and metamyelocytes one per cent. Staining of the leukocytes for alkaline phosphatase gave a score of 18 (normal value 15-100). Aspiration of sternal marrow yielded a cellular sample with megakaryocytic hyperplasia. Serum lactic dehydrogenase was increased at 1000 units. There was no evidence of occult gastrointestinal bleeding.

During the first week of admission the patient's hematoma gradually decreased in size, but both the platelet and white cell counts remained elevated. Treatment was commenced with 2 mgs. uracil mustard daily and continued for 25 days. This resulted in a fall in both the platelet and white cell counts to normal (Fig. 1). The spleen, however, remained palpable. Measurement of the patient's red cell mass two months after admission using $^{51}$Cr labelled red cells gave a value of 30.0 ml./Kg. (normal range 22-29 ml./Kg.).
During the next seven months the patient remained well and received no further chemotherapy. She had no more hematomata and was little troubled by bruising. However, at this time, a further two-week course of uracil mustard was given as the platelet count had risen to over 1,000,000 per cu. mm. and the WBC to 25,400 cu. mm. There was again a prompt fall in the platelet count to 150,000 cu. mm.

Case 2. This patient was a 70-year-old man who had had a Polya gastrectomy 16 months previously because of a duodenal ulcer. Since then he had been persistently anemic despite taking oral iron and on one occasion had required transfusion. On admission he complained of lassitude, sore tongue and difficulty in swallowing. He had marked koilonychia, a smooth tongue and his spleen was enlarged ½ inch below the left costal margin. His hemoglobin was 6.2 Gm./100 ml.; hematocrit, 24 per cent; MCHC 26 per cent; MCV 72 cubic microns. The platelet count was 1,340,000 cu. mm.; WBC, 13,700 cu. mm. with a differential count of neutrophils 71 per cent, eosinophils three per cent, lymphocytes 22 per cent, monocytes four per cent. A bone marrow aspirate was hypercellular but without predominance of any single cell line. There was no stainable iron present in the sample. Serum iron was 15 μg./100 ml., but the serum levels of B₁₂ and folate were normal. His stools gave a negative reaction for occult blood and a barium meal showed no evidence of stoma ulceration. A barium swallow was also normal.

The patient was discharged following a course of intramuscular iron during which his hemoglobin rose to 9.0 Gm./100 ml. (Fig. 2). While at home, the patient continued to take oral iron but when seen two weeks later his hemoglobin had fallen to 7.1 Gm./100 ml. and he was in congestive cardiac failure. Both the platelet and white cell counts remained elevated. There was again no indication of gastrointestinal bleeding or laboratory evidence to suggest that hemolysis had occurred. He was transfused with disappearance of the signs of cardiac failure.

Two weeks later the patient felt better and his dysphagia had gone but he now had signs of a venous thrombosis in his right leg. The hemoglobin had been well maintained but the platelet count had risen to 3,280,000 cu. mm. Treatment with 2 mg. uracil mustard
Fig. 2.—Case 2. Polycythemia vera with thrombocytemia. Response to uracil mustard (U.M.).
Fig. 3.—Case 4. Chronic myeloid leukemia. Failure of busulphan to control thrombocythemia. Satisfactory response to uracil mustard.
was given daily for four weeks. A week after the drug was stopped the platelet count had fallen to 163,000 cu. mm. and the white cells to 4,550 cu. mm. Following treatment the patient reported an increased sense of wellbeing, improved appetite and there were no further episodes of thrombosis. His spleen, however, remained just palpable.

During the following 12 months no further chemotherapy to reduce the platelet count was required, but at this time a mild polycythemia developed which was treated by venesection.

Case 3. A 56-year-old female presented with symptoms of weakness, excessive sweating and a tendency to bruise easily. She was plethoric and the spleen was palpable two inches below the costal margin. The hemoglobin was 17.5 Gm./100 ml.; hematocrit, 58 per cent; WBC, 22,600 cu. mm. with 84 per cent neutrophils. Platelets were 1,400,000 cu. mm. A diagnosis of polycythemia vera was made and she was treated by venesection and was given two doses of 5 mC. radioactive phosphorus, there being an interval of three months between each dose. The patient's symptoms markedly improved three months after the second dose when the hemoglobin had fallen to 14.1 Gm./100 ml. and the hematocrit to 47 per cent. Measurement of the red cell mass using $^{51}$Cr labeled red cells at this time gave a normal value of 28.1 ml./Kg. The initially high platelet count fell to 440,000 cu. mm. six weeks after the second dose of phosphorus but six months later had risen to 1,300,000 cu. mm. The patient's previous symptoms recurred with return of the thrombocythemia although there had been no increase in the hemoglobin or hematocrit.

Treatment was then started with 2 mg. uracil mustard daily. Within seven weeks the platelet count had fallen to 169,000 cu. mm. and the patient again lost her symptoms. Following discontinuation of the uracil mustard the platelet count remained below 500,000 cu. mm. for the next 15 months, when her condition quickly deteriorated and she died showing the features of malignant myelofibrosis.

**Chronic Myeloid Leukemia**

Case 4. This 23-year-old female was admitted to hospital in September, 1964 with a five-week history of loss of energy and increasing pallor. Her spleen was enlarged to below the umbilicus. A blood count showed: Hemoglobin, 5.7 Gm./100 ml.; hematocrit, 25 per cent; platelets, 320,000 cu. mm.; WBC, 160,400 cu. mm. with blasts four per cent, promyelocytes two per cent, myelocytes 2 per cent, neutrophils 48 per cent, eosinophils two per cent, basophils six per cent, lymphocytes two per cent, monocytes 18 per cent. There were 11 normoblasts per 100 white cells. The mature neutrophils gave a negative reaction when stained for alkaline phosphatase. A bone marrow aspirate yielded a cellular sample showing a myeloid hyperplasia in keeping with a diagnosis of chronic myeloid leukemia.

Following transfusion, treatment was commenced with busulphan, 6 mg. daily, with satisfactory subjective improvement and fall in the white cell count (Fig. 3). The spleen became impalpable. The busulphan dose was reduced to 2 mg. daily, which maintained the white cell count in the region of 10,000 cu. mm. with a platelet count ranging up to 400,000 cu. mm. There followed, then, a gradual increase in the platelet count so that by the 19th month of the disease they numbered 1,754,000 cu. mm. The thrombocythemia was associated with a rise in the white cells reaching 28,000 cu. mm. of which only four per cent myelocytes and five per cent metamyelocytes were immature forms. At this time the patient complained of lassitude, but symptoms due to thrombosis or hemorrhage did not occur. The rise in the platelet count was treated by increasing the dose of busulphan up to a maximum of 6 mg. daily. However, after six weeks it was found necessary to stop the drug as the white cell count had fallen to 6,000 cu. mm. The thrombocythemia on the other hand, was little affected, the platelet count falling only to 1,000,000 cu. mm. and rising quickly two weeks later to 1,575,000 cu. mm. Treatment with uracil mustard was then commenced, starting with a dose of 2 mg. per week increasing gradually over a period of nine weeks to 2 mg. daily. The platelet count gradually declined to 440,000 cu. mm. after 13 weeks treatment. The white cell count was not as responsive to the drug and remained in the region of 35,000 cu. mm. until the dosage of uracil mustard was later increased to 4 mg. daily, the count then falling to 7000 cu. mm.
Thirteen months after the institution of uracil mustard therapy the patient died from an acute blastic transformation of her disease.

Hemorrhagic Thrombocytaphemia

Case 5. An 18-year-old male was admitted to hospital because of severe headache and vomiting. His symptoms quickly improved after admission and were considered to be due to migraine. It was noted, however, that both his liver and spleen were enlarged a quarter inch below the costal margin. There was no history of abnormal bleeding. The blood count was: Hemoglobin, 12.7 Gm./100 ml.; hematocrit, 39 per cent; platelets, 1,110,000 cu. mm.; WBC, 10,300 cu. mm. (neutrophils 82 per cent, lymphocytes 11 per cent, monocytes two per cent, metamyelocytes two per cent, myelocytes three per cent). The neutrophil alkaline phosphatase score was 74 and within the normal range. A bone marrow aspirate and trephine biopsy showed the presence of marked megakaryocytic hyperplasia (Fig. 4). Serum lactic dehydrogenase activity was 1600 units. A liver biopsy showed no abnormality and no evidence of extramedullary hemopoiesis. The patient was considered to be suffering from hemorrhagic thrombocytaphemia but was discharged from the hospital without treatment to reduce the high platelet count. He was advised to take an ergotamine preparation for his migraine.

He was next seen four months later because of severe headache accompanied by vomiting. The attack had been preceded by visual disturbances characteristic of migraine. Since his previous admission he had been well, apart from fairly frequent headaches which had been unresponsive to ergotamine. Because of its ineffectiveness he had taken very little of the drug and indeed, had stopped it completely soon after discharge. On examination, hepatosplenomegaly was again noted and the blood count was also similar to that found during the previous admission, the platelet count being 1,500,000 cu. mm. His symptoms of headache and vomiting again quickly settled while in hospital. Although he gave no history of chest pain or of exertional dyspnea, an electrocardiogram was taken and this showed marked abnormality with evidence of posterolateral myocardial ischemia (Fig. 5).

On discharge, treatment was commenced with 2 mg. uracil mustard daily, the drug being stopped after four weeks, the platelet count then having begun to decline. After a further three weeks the platelets numbered 265,000 cu. mm.

When seen 19 weeks following the termination of chemotherapy, the patient felt well and had had no further headaches. His liver and spleen were still palpable but were reduced in size. The platelet count was 562,000 cu. mm. Two further electrocardiograms have been taken, the first showed a marked improvement in the abnormality, and the second a completely normal tracing (Fig. 6).

**DISCUSSION**

Despite many studies, it is still not clear why patients with thrombocytaphemia should suffer from hemorrhages as well as thromboses. However, in two of the
Fig. 5.—Electrocardiogram showing evidence of posterolateral myocardial ischemia.
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Fig. 6.—Case 5. Normal electrocardiogram 19 weeks after uracil mustard therapy.
present cases, episodes of bleeding or thrombosis ceased when the platelet count was reduced by chemotherapy, and in another patient (Case 5), the electrocardiographic signs of myocardial ischemia regressed completely following treatment.

A variety of agents have been used in the treatment of thrombocythemia. In earlier accounts whole body irradiation, mechlorethamine, urethane and triethylene melamine were all used with varying results. In the more recent literature and in standard hematological texts, either busulphan or radioactive phosphorus is now generally employed to reduce the platelet count. However, neither of these therapies have been found to be wholly satisfactory. Radioactive phosphorus requires special facilities for its handling which are not everywhere available. Furthermore, there is evidence that when it is used in the treatment of polycythemia vera it may promote the development of an acute leukemia. Such a risk could also be expected to apply to its use in hemorrhagic thrombocythemia as these patients may also survive many years. Again, by no means do all patients respond to radioactive phosphorus or busulphan. In a recent report it was found that two of eight patients with hemorrhagic thrombocythemia failed to achieve remission when treated with busulphan as did one of six who were treated with phosphorus. Also, in order to produce a remission with busulphan, the average duration of treatment required was as long as three months.

Uracil mustard proved to be effective in reducing the platelet count in all of the present five patients. In four an average of just over five weeks elapsed before the count became normal. It took longer to reduce the platelet count in the patient with chronic myeloid leukemia, as the dose was only gradually increased. In three patients the platelets remained below 1,000,000 cu. mm. for five, 12 and 15 months without further therapy. In another patient a second course of uracil mustard was required seven months after the initial treatment while the patient with leukemia was maintained on the drug. The associated high white cell counts were also reduced by uracil mustard, although in Case 5 a mild leucopenia was produced. In the patient with chronic myeloid leukemia uracil mustard was of value in reducing a thrombocythemia resistant to the largest dose of busulphan which the patient could tolerate without undue depression of the white cell count. That uracil mustard may also be effective in treating a high platelet count which has failed to respond satisfactorily to radioactive phosphorus is shown by Case 3. Although only a short-lived reduction in the platelet count followed two doses of phosphorus, a single course of uracil mustard produced a long-lasting remission.

The present series of cases is small but the results obtained indicate that uracil mustard is effective in reducing a high platelet count and suggest that it may be superior to busulphan and have advantages over radioactive phosphorus for this purpose. Certainly, further trials of the drug in the treatment of thrombocythemia are indicated.

**SUMMARY**

Five patients with thrombocythemia are described. All were successfully treated with uracil mustard including two who were resistant to busulphan or
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radioactive phosphorus. Uracil mustard reduced the platelet count quickly and a single course of the drug produced a satisfactory remission without undue marrow depression. The results are compared with those which have been obtained with busulphan and radioactive phosphorus. It is concluded that uracil mustard may prove to be the most effective, convenient and possibly the safest, means of treating thrombocythemia.

REFERENCES

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