PAPERS AND ORIGINALS

Leukostasis associated with blood transfusion in acute myeloid leukaemia

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Summary and conclusions

Three patients with acute myeloblastic leukaemia and blast cell counts greater than $100 \times 10^9/l$ ($100\,000/mm^3$) died unexpectedly soon after blood transfusion. In two cases postmortem examination disclosed cerebral leukostasis. Analysis of the records from the MRC's fourth and fifth acute myeloid leukaemia trials showed that in the first week after diagnosis mortality was five times greater in patients with blast counts above $100 \times 10^9/l$ than in patients with lower counts. Age and platelet count did not explain this excess. The mean haemoglobin concentration in the patients with high blast counts who died within the first week was 10.5 ± 2.8 g/dl, which was significantly higher than that in the surviving group (7.6 ± 2.4 g/dl). Only half the patients received chemotherapy within two days of diagnosis.

Leukostasis is an important cause of early death in patients with high blast counts, and the increase in viscosity produced by transfusing to a haemoglobin concentration above 10 g/dl may lead to sudden deterioration. Transfusion to such concentrations should be avoided until the blast count has been reduced by early chemotherapy.

Introduction

Many patients with acute myeloid leukaemia die before an adequate trial of chemotherapy has been completed.¹ The main causes of death are infection and haemorrhage,^{2,3} although vascular occlusion with myeloblasts (leukostasis) may cause central nervous,⁴ pulmonary,⁵ and cardiac⁶ effects. Deaths from

leukostasis are unusual in patients with blast cell counts less than $100 \times 10^9/l$ ($100\,000/mm^3$),⁷ and whole-blood viscosity is rarely increased in patients with high counts because of a concomitant reduction in haemoglobin concentration.⁸ In the MRC's fourth and fifth leukaemia trials patients with blast counts exceeding $50 \times 10^9/l$ had a higher mortality in the first six weeks. Generally, deaths from leukostasis would be expected to occur in the first few days of treatment, before a maximal reduction in the blast count.

I describe here three patients who presented with blast cell counts exceeding $100 \times 10^9/l$ who died from leukostasis shortly after receiving blood transfusions. I also present the results of an analysis of the forms from the fourth and fifth trials to see whether the increased mortality in patients with high blast counts was mainly due to early deaths and whether early deaths were related to hyperviscosity produced by a high haemoglobin concentration or blood transfusion.

Methods

Three groups of patients were compared for full blood count at diagnosis, number of blood transfusions received, time from diagnosis to the start of chemotherapy, and age. The first group comprised all patients with blast counts exceeding $100 \times 10^9/l$ who died within seven days after diagnosis; the second comprised patients with blast counts below $100 \times 10^9/l$ who died within seven days after diagnosis; and the third comprised patients with high blast counts who survived the first week.

CASE REPORTS

Case 1—A 36-year-old man had a four-week history of weakness and shortness of breath. He had had angina and blurred vision two days before admission. He was pale and alert, with a temperature of 39°C. He had shotty lymph nodes in the neck and bilateral fundal haemorrhages but no purpura. Haemoglobin was 5.7 g/dl, platelet count $97 \times 10^9/l$, and blast count $196 \times 10^9/l$. Bone marrow aspiration confirmed acute myeloid leukaemia. He was treated with carbenicillin and gentamicin intravenously and transfused with four units of packed red cells. The next afternoon he became more breathless and confused, but there was no evidence of heart failure or bronchopneumonia. He developed right hemiplegia and became comatose, dying later that

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Cerebral vessels with intravascular leukostasis. One vessel (arrowed) is surrounded by masses of blast cells and fresh haemorrhage. (H and E. $\times 148$.)

night. A full blood count, taken when he was receiving his third unit of packed red cells, showed a haemoglobin concentration of 9.3 g/dl and blast count of $202 \times 10^9/l$. Although the platelet count had fallen to $50 \times 10^9/l$, there was no evidence of fresh bleeding. *Escherichia coli* was isolated from blood taken post mortem. At necropsy, the brain showed multiple circumscribed haemorrhagic areas surrounding oval grey nodules. These were masses of leukaemic cells associated with remnants of blood vessels filled with blast cells (see figure). The arteries and veins in the lungs were also occluded by masses of leucocytes entrapped in organised fibrin.

Case 2—A 33-year-old woman presented with a six-week history of sore throat, weight loss, and night sweats. She was pale and feverish, with rapid respiration. She had hepatosplenomegaly and ecchymoses on her limbs. Haemoglobin was 8.7 g/dl, blast count $258 \times 10^9/l$, and platelet count $45 \times 10^9/l$. On the day of admission three units of blood were transfused; the next day chemotherapy with daunorubicin and cytosine arabinoside (cytarabine) was started. The patient became confused and comatose, however, and died shortly after. Her haemoglobin concentration after transfusion was 10 g/dl, and the platelet count had fallen to $20 \times 10^9/l$. At necropsy a right cerebral haemorrhage was visible macroscopically. Histology of the brain showed numerous myeloblasts within the blood vessels and an area of infarction adjacent to the haemorrhage. The lungs showed dilated capillaries, with leukaemic infiltration, leukaemic thrombi, and small areas of infarction.

Case 3—A 63-year-old man was admitted with a three-week history of effort dyspnoea and pleuritic pain. He was tachypnoeic but not orthopnoeic. His temperature was 37.9°C , and he had bilateral basal crepitations. There was purpura on his chest, and he had ulcerated gums and tonsils. Peripheral pulses were present. Blood film showed acute myeloblastic leukaemia, with blast count $340 \times 10^9/l$, haemoglobin 10.3 g/dl, and platelet count $18 \times 10^9/l$. Serum potassium concentration was 2.5 mmol (mEq)/l. The patient was treated with intravenous cephaloridine, frusemide, and intravenous potassium chloride. Blood transfusion of four units was started and chemotherapy with daunorubicin and cytosine arabinoside given. Over the next 24 hours the crepitations improved but he became increasingly dyspnoeic, centrally cyanosed, and confused. Haemoglobin was 13.8 g/dl, blast count $108 \times 10^9/l$, and platelet count $10 \times 10^9/l$. He complained of numbness in his left leg, and the femoral, popliteal, and dorsalis pedis pulses were indetectable. He became comatose and died. Permission for necropsy was not obtained.

Results

Table I gives the number of patients who died in the first week after diagnosis. Patients with blast counts exceeding $100 \times 10^9/l$ had a mortality of 25% compared with 5% in the group with lower blast

TABLE I—Numbers of patients dying in first week after diagnosis

Blast count	No (%) of patients dying	No (%) of patients surviving	No of deaths each day in first week						
			Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
$>100 \times 10^9/l$	11 (25)*	33 (75)	1	6	1	1	1		1
$<100 \times 10^9/l$	14 (5)	267 (95)	2	1	3	4	3		1

* $P < 0.001$ by χ^2 test.

counts. Since increasing age and low platelet count are adverse prognostic factors they were compared between the three groups of patients. Table II shows that there was no difference in mean ages but that the mean platelet count in the patients with low blast counts who died within a week was significantly lower than in patients with high blast counts.

The main difference between patients with high blast counts who died early and those who survived was in haemoglobin, the concentration in the survivors being significantly lower (table III). Blood transfusion was not given more often to patients who died early, since they had a higher haemoglobin concentration. Table III shows that in most of the survivors haemoglobin was less than 10.5 g/dl when the blast count was over $100 \times 10^9/l$.

The three patients who survived with high haemoglobin concentrations were all treated on the day of diagnosis. Only one of the 11 patients dying early with a high blast count received chemotherapy on the day of diagnosis, although 10 received chemotherapy. Only half the patients were given chemotherapy within the first two days after diagnosis. Because the initial haemoglobin concentration in the survivors was low, by the time it had risen to at least 10.5 g/dl the peripheral blast counts had fallen to below $50 \times 10^9/l$, despite the delay in giving chemotherapy.

Table IV gives the main causes of death. Neurological deterioration was the most common cause in both the high and low blast count groups. Necropsy reports were available on three patients who died with high blast counts, one of whom is reported as case 2. A limited report only was available on one, which showed that blood vessels in the lung had 90% of their lumina occupied by blast cells. In the re-

TABLE II—Mean age and numbers of patients with high or low platelet count according to blast count. Patients with low blast counts who survived are excluded

	Blast count $>100 \times 10^9/l$		Blast count $100 \times 10^9/l$
	Patients dying within a week (A)	Survivors (B)	Patients dying within a week (C)
Mean age in years ($\pm$ SD)	48.2 ± 15.8	45.8 ± 19.7	48.1 ± 19.3
No (%) with platelet count $10 \times 10^9/l$ *	2 (9)	8 (24)	8 (57)
No (%) with platelet count $>10 \times 10^9/l$	10 (91)	25 (76)	6 (43)

* (A) v (C): $P = 0.034$, Fischer's exact test; (A) v (B): NS.

TABLE III—Mean haemoglobin concentrations in patients with high blast counts and numbers receiving transfusions

	Mean haemoglobin concentration $\pm$ SD (g/dl)	No of patients	No (%) receiving transfusion	No (%) of patients with haemoglobin concentration >10.5 g/dl
Survivors	7.6 ± 2.4 *	33	20 (61)	3 (9)*
Early deaths	10.5 ± 2.8	11	4 (36)	8 (73)

* $P < 0.005$, unpaired t test.

†All treated on day of diagnosis.

TABLE IV—Causes of death and numbers of patients dying within a week after diagnosis

Blast count at diagnosis	Neurological deterioration (No with haemorrhage elsewhere)	Infection	Melaena	Metabolic acidosis	Myocardial infarct
$>100 \times 10^9/l$	8 (2)	2		1	
$<100 \times 10^9/l$	8 (6)	4	1		1

maining patient haemoglobin was 13.7 g/dl on presentation, blast count $160 \times 10^9/l$, and platelet count $18 \times 10^9/l$. He had a cerebral haemorrhage with intravascular leukostasis.

Discussion

A previous necropsy study⁷ of patients dying with high blast cell counts showed that leukaemic thrombi and aggregates were most commonly found in the lungs and brain and were unusual in patients with blast counts below $100 \times 10^9/l$. Often patients became confused and dyspnoeic shortly before death. Nevertheless, unless postmortem examinations are performed, cerebral haemorrhage due to leukostasis is difficult to distinguish from that due to low platelet counts. The results of the fourth and fifth MRC trials showed that patients with high blast counts have a greatly increased early mortality, which cannot be accounted for by other high-risk factors. In the few patients on whom necropsy was performed leucocyte aggregates were found in the areas seen clinically to be affected. The cause of these aggregates is not clear, but the viscosity of whole blood with high blast counts is 75% greater than expected from the packed cell volume (PCV).⁸ The viscosity of leukaemic-cell suspensions is only slightly greater than that of red cells of the same PCV. Leukaemic cells are much less deformable than red blood cells,⁹ and the pressure required to force nondeformable cells through filters increases with increasing PCV.⁹ Most patients with leukaemia and a high blast count have a low haemoglobin concentration on presentation, and thus the actual viscosity is no greater than that of a normal PCV of 0.47 (47%). In the patients who died within a week, however, the haemoglobin concentration was significantly higher than in the survivors. Since viscosity is log-linearly related to PCV throughout the range of PCV these patients would have had a higher whole-blood viscosity. Thomas *et al.*¹⁰ showed that a small change in PCV in the normal range could produce a 50% change in cerebral blood flow. The combination of a viscosity greater than expected for a given PCV together with rigid blast cells may have led to leukostasis. The three patients described deteriorated rapidly on transfusion to haemoglobin concentrations of at least 10 g/dl, and although necropsy was not carried out in case 3, leukostasis was the most likely explanation of the clinical events.

The platelet count in the reported cases fell over the 24 hours after admission. This was unlikely to have been due to chemotherapy, and there was no bleeding from venepuncture sites or fresh haemorrhage such as may occur with disseminated intravascular coagulation, although blood cultures were positive in one patient. The fall in platelet count could have led to cerebral bleeding, but the postmortem examinations showed leukostasis as described by Freireich *et al.*¹ Alternatively, the fall could have been produced by haemorrhage associated with leukostasis consuming platelets. In either case it would have predisposed to further bleeding in areas of leukostasis.

As patients with high blast counts whose disease went into remission survived as long as those with lower counts,¹ it is important to prevent these early deaths. A haemoglobin concentration above 10 g/dl is an adverse risk factor. Transfusing patients to this concentration before their blast count has been reduced should be avoided as it may lead to early death by encouraging leukostasis. The only survivors whose haemoglobin concentration was over 10 g/dl had received chemotherapy on the day of diagnosis. Conventional chemotherapy halved the blast count within 24 hours in most patients and should be started as a matter of urgency.

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Reversal of clofibrate-induced cholesterol oversaturation of bile with chenodeoxycholic acid

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Summary and conclusions

Giving clofibrate 2 g daily to seven patients significantly increased the biliary cholesterol concentration while the proportion of bile acids fell. Five patients on established clofibrate treatment were given 750 mg of chenodeoxy-

cholic acid (CDCA) daily for one month. Biliary lipid analysis after the CDCA treatment showed a significant fall in the proportion of cholesterol and a rise in that of bile acids. The serum lipid concentrations, which had already been reduced by diet and clofibrate, showed a further significant reduction after the introduction of CDCA.

This study suggests that CDCA may be usefully combined with clofibrate to reverse the tendency towards cholesterol saturation of bile and enhance the effect of lowering serum lipid concentrations.

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Introduction

Clofibrate is used extensively for hyperlipidaemia and is effective and palatable. It acts on the liver to enhance the biliary