THE USE OF GRANULOCYTE TRANSFUSION

A Case Report

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SUMMARY: Methotrexate in conventional low dosage is highly effective in treating Choriocarcinoma. We report a patient in whom oral methotrexate and probenecid together produced a severe toxic reaction necessitating the transfusion of white blood cells and platelet concentrates. The place of white cell concentrates in Military Hospital transfusion practice is discussed.

Introduction

The incidence of infection in neutropenic patients rises as the peripheral blood neutrophil count falls¹. Clinical results of granulocyte transfusions have been published from several centres and there is little doubt that the procedure is effective in the treatment of infected neutropenic patients². Accordingly facilities for collecting white cells are becoming widely available and clinicians are making freer use of the procedure. This case report illustrates that provision of white cell concentrates may be necessary in a unit where cytotoxic drugs are administered and raises the question of whether such concentrates can reasonably be provided in the context of a Military Hospital.

Case report

A 31 year old woman, with 12 week amenorrhoea was admitted to hospital bleeding per vaginam. An ultrasonic scan demonstrated a hydatiform mole. Expulsion of the mole was induced and dilatation and curettage performed.

During the next four weeks her urinary human chorionic gonadotrophin (HCG) level remained elevated, and intermittent vaginal bleeding continued. Repeat endometrial curettage revealed hydatidiform villi.

She was treated initially with methotrexate 15 mg IM daily for five days, with no ill effects. However, as the high HCG level persisted (Table I), 19 days later she was given a second five day course, this time of oral methotrexate 12.5 mg daily with probenecid 500 mg twice daily.

The next day she became acutely ill with mouth, throat and anal ulceration, a pyrexia of 40°C and a widespread erythematous skin rash. Her neutrophil count fell to $0.255 \times 10^9/l$ and liver function tests showed evidence of hepato-cellular damage (Table I). Blood, urine, sputum and throat cultures demonstrated no pathogens. Marrow biopsy showed marked hypoplasia of the myeloid series with little active thrombopoiesis.

Reverse barrier nursing was instituted, intravenous folinic acid, cephaloridine, carbenicillin and hydrocortisone were given. Tetracycline with nystatin was used as a mouthwash. Combined platelet and granulocyte concentrates, prepared from random German Army donors using a Latham Separator (Haemonetics Model 30), were transfused. Her condition improved and the pyrexia settled but the neutro-

Table I
Relationship between cytotoxic therapy and neutrophil count,
urinary excretion of HCG and serum gamma glutamy transpeptidase

Date	Neutrophil count x 10 ⁹ /l	HCG in urine IU/24 hr	Gamma G T IU/l
6.4.78		16.000	
11.4.78		21.000	
13.4.78	3.264		18
14.4.78		21.700	
19.4.78		27.650	
20.4.78	4.745		
21.4.78		16.800	
2.5.78		20.000	
16.5.78		NIL	
17.5.78	1.891		
18.5.78.	0.255		14
19.5.78	0.798		
20.5.78	0.616		
21.5.78	0.884	NIL	100
22.5.78	0.748	NIL	
24.5.78	0.600		
26.5.78	0.952		47
27.5.78	0.510		
29.5.78	4.125		
31.5.78	5.250		
1.6.78	4.950		
5.6.78	5.724		188
12.6.78	8.446		42
19.6.78	4.851		
30.6.78			37

Drugs and therapy given (inclusive dates)	
Methotrexate	18.4.78 — 22.4.78 and 11.5.78 — 15.5.78
Probenecid	11.5.78 — 15.5.78
Granulocytes transfusions	18.5.78 — 29.5.78 Daily
Folinic acid	16.5.78 — 20.5.78
Bone marrow, biopsies, perform on	16.5.78 and 29.5.78

penia and thrombocytopenia persisted for 15 days, when neutrophil count rose to $4.1 \times 10^9/l$ and platelets to $124 \times 10^9/l$. A repeat marrow biopsy confirmed active myelo and thrombopoiesis; the transfusions were discontinued.

Shortly afterwards diffuse hair loss was noticed, which proceeded to complete alopecia. The mouth and throat ulceration persisted for a further four weeks and recovery was complicated by a deep vein thrombosis. She was fit for discharge six weeks after her last dose of methotrexate.

Discussion

This patient suffered a life-threatening toxic reaction to her second course of methotrexate. The severity of the reaction was probably determined by sustained exposure to the drug caused by probenecid delaying renal excretion^{3,4}. It is appropriate to consider the implications of the treatment which this patient required, as the increasing use of cytotoxic drugs in many specialities imposes the responsibility to provide granulocyte support in the event of marrow failure.

The consensus is that for clinical benefit a daily infusion of at least 2×10^{10} cells is required⁵. This is equivalent to the white cell content of about 10 units of fresh blood. A method of processing large volumes of blood and concentrating the white cells is thus required. Several techniques have been developed and the choice is dictated mainly by economic considerations. Expensive intermittent or continuous flow cell separators, as used in Munster, can only be justified where versatility is needed to perform large volume plasma exchanges, or to separate acute leukaemia cells for immunotherapy⁵.

Where granulocyte transfusion is the only function required, the method of choice is filtration leucapheresis (Leukopak, Fenwal Laboratories), which can produce a good yield from a normal donor at low cost. Unfortunately the procedure requires that the donor be heparinized. To increase the yield of granulocytes, steroids are often administered before donation and a sedimenting agent such as dextran and hydroxy-ethyl starch is used to improve separation. It has been suggested that interaction between the plasma and nylon wool filters may activate complement and also that the procedure damages the leucocytes collected, liberating some of their content and impairing their function after transfusion⁶. The donor may consequently suffer occasional pyrogenic and urticarial reactions, but there is no report of death resulting from leucapheresis.

Although the contingency of marrow failure may be remote, access to facilities for granulocyte transfusion must be available in units undertaking cytotoxic therapy. Leucapheresis is clearly a more hazardous procedure than donating a single unit of blood¹, and even though the equipment is readily available at low cost, and we have sufficient expertise to supervise both the donation and transfusion procedures, serious consideration must be given to the ethics of administering drugs and anticoagulants to healthy soldiers, even with their informed consent.

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