Acute refractory congestive cardiac failure following allogeneic bone marrow transplantation

A case report

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Summary

A young woman aged 18 years underwent allogeneic bone marrow transplantation for severe acute aplastic anaemia. In the 3 weeks following this procedure the platelet count remained between 10 and 30 x 10^9/L, and from the 21st day after the transplant there was relentless progression of congestive cardiac failure resulting in the patient's death 4 days after its onset. Autopsy showed widespread subendocardial haemorrhage and extensive bleeding between the myocardial fibres resulting in refractory cardiac failure. These findings are compatible with drug-induced cardiotoxicity.

Severe acute aplastic anaemia is a rapidly progressive disease, the majority of patients dying from infection or haemorrhage within the first 6 months. It has been demonstrated that where a suitable donor is available allogeneic bone marrow transplantation is a statistically superior form of treatment to conservative management with corticosteroids and anabolic androgenic hormones.

In the period immediately after the transplant, prior to engraftment, the patients are granulocytopenic and thrombocytopenic, and the availability of allogeneic white cell and platelet support has reduced the hazard of infection and haemorrhage. Among the other complications that arise and may be related to multi-agent chemotherapy or total body irradiation are veno-occlusive disease of the liver and severe refractory congestive cardiac failure characterized by fibrin microthrombi and intramyocardial haemorrhage. We report a further example of the latter complication occurring 21 days after successful bone marrow transplantation.

Case report

An 18-year-old nurse presented with a 1-week history of dizziness, weakness and malaise with dyspnoea on exertion. There was associated menorrhagia, but her previous menstrual cycle had been normal. Easy bruising and inappropriate bleeding had developed in the course of the preceding 2 weeks.

On examination the patient was pale and apyrexial. There was bruising around both eyes, but no other cutaneous bleeding was evident. Both optic fundi showed haemorrhages and exudates.

Initial laboratory studies revealed a haemoglobin value of 5 g/dl; the granulocyte count was < 1 x 10^9/L and the platelet count < 10 x 10^9/L. The reticulocyte count was 0.6% corrected for the degree of anaemia. Bone marrow aspiration and trephine biopsy revealed aplasia. The biochemical profile, serum electrolyte levels, renal and cardiac function, ECG and chest radiographs were normal.

The haematological features were diagnostic of severe acute aplastic anaemia, and the family was accordingly screened for a bone marrow donor. The results of tissue typing and mixed lymphocyte culture (Table I) showed HLA identity with N.V., but reactivity in mixed lymphocyte culture. Conversely, Pa.V. was only haplo-identical but MLC non-reactive. These results suggest that the patient (Ch.V.) had a recombination between serologically determined HLA A and B loci and the HLA D locus on the maternally derived chromosome.

In view of the gravity of the established clinical diagnosis and the uncertainty as to whether serologically or lymphocyte-determined antigens are of predominant importance in predicting the success of bone marrow transplantation, the

| Table I. Results of HLA Phenotype and Unilateral MLC Testing |
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| **HLA phenotype** | **Ch. V.** | **Pa. V.** | **Ca. V.** | **Pl. V.** | **N. V.** |
| Ch. V. (recipient) | A10(34), B12, W15 | A2, 28 | A2, 28 | A2, 28 | A10(34), B12, W15 |
| Pa. V. | xxx | xxx | xxx | xxx | xxx |
| Ca. V. | A2, 28 | B12, 14 | A2, 28 | B12, 14 | A2, 28 |
| Pl. V. | A2, 28 | B5, 14 | A2, 28 | B5, 14 | A2, 28 |
| N. V. | A10(34), B12, W15 | A10(34), B12, W15 | A10(34), B12, W15 | A10(34), B12, W15 | A10(34), B12, W15 |

*Results expressed as a stabilized relative response (SRR) represented on an arbitrarily graded scale (see below) in order to make these results analogous to the serological typing (as recommended in the Joint Report (MLC) from the 6th International Histocompatibility Workshop Conference, Histocompatibility Testing). SRR scoring code: xxx < 20; xx < 30; x < 40; xxx < 50; (+) < 60; -? < 70; — > 70.
procedure was undertaken with informed consent from the HLA haplo-identical but MLC non-reactive sibling (Pa.V.).

The transplant day was designated 0 (Fig. 1). Conditioning for the procedure was commenced on day -9 with 3 daily intravenous infusions of procarbazine 12.5 mg/kg on alternate odd days (days -9, -7 and -5), and 3 daily intravenous infusions of antilymphocyte globulin 7 mg/kg on even days (days -8, -6 and -4). Twenty-four hours after a priming dose of white cells and platelets collected by continuous-flow centrifugation the patient received cyclophosphamide 50 mg/kg commencing on day -5, administered intravenously on 4 consecutive days, with attention to adequacy of hydration and maintenance of electrolyte status. After a 24-hour rest period she was infused with 2.4 X 10⁶ nucleated cells per kg from the donor.

On the first 5 days after the transplant she also received Buffy layer from the donor. On the 6th day after the transplant a temperature between 39° and 40°C was recorded, and after repeated blood cultures had been taken a combination of cephalothin 12 g, gentamicin 240 mg and carbenicillin 30 g was administered intravenously every day. The aminoglycoside peak and trough levels, as well as renal function, were regularly monitored and the dose was adjusted where necessary.

During the first 2 weeks the patient’s course was relatively uncomplicated, although the pyrexia was poorly controlled despite antibiotics and allogeneic white cell support.

Because the anticipated increase in the white cell and platelet counts had not occurred in the 3rd week after the transplant, aspiration and trephine biopsy were carried out on day 19; this showed morphological evidence of engraftment. On the 21st day of cyclophosphamide administration in patients undergoing course and a high mortality rate attributable to thrombocytopenic bleeding and infections consequent upon marked granulocytopenia. In these patients controlled randomized studies have demonstrated a statistically significant advantage for bone marrow transplantation over conventional treatment with anabolic androgens and immunosuppressive drugs such as the corticosteroids.

In the patient who has undergone a transplant additional complications arise. Appelbaum et al. reported acute lethal myopericarditis in 4 out of 15 patients receiving high-dose combination chemotherapy, including cyclophosphamide 45 mg/kg/d for 4 days, occurring 5 - 9 days after the initiation of chemotherapy. In 3 of the 4 patients on whom autopsy was performed the heart was increased in weight, and histological examination showed intramyocardial extravasation of blood.

Evidence for the incineration of cyclophosphamide in the genesis of the cardiac lesion comes from canine studies in which infusion of a single dose of cyclophosphamide 500 mg/kg intravenously resulted in a marked fall in the voltage of the QRS complex after 2 - 3 hours and in death from pulmonary oedema and intractable cardiac failure in a further 30 minutes.

Although our patient developed congestive cardiac failure 21 days after the transplant and 26 days after beginning cyclophosphamide infusion there are notable similarities with the 4 cases reported by Appelbaum et al., including dosage, duration of cyclophosphamide therapy and clinical and histological findings.

Buja et al. reported on the cardiac lesions in 22 patients at autopsy after bone marrow transplantation. The vast majority of findings, such as cardiomegaly and haemorrhage, were nonspecific. It is relevant that essentially similar changes were present in those dying from their underlying disease process who were not treated by bone marrow transplantation. However, in 2 patients there were specific changes of intramyocardial haemorrhage which the authors felt were possibly induced by cyclophosphamide.

Although our case is in many respects similar to those reported by Appelbaum et al. and Buja et al., we cannot exclude coexisting septicaemia or thrombocytopenia as having contributed to the cardiac lesions. In terms of practical management cardiotoxicity, which may be lethal, must now be added to haemorrhagic cystitis and the syndrome of inappropriate secretion of antidiuretic hormone as complications of cyclophosphamide administration in patients undergoing bone marrow transplantation.

We thank the South African Medical Research Council and the University of Cape Town Leukaemia Centre for their support, Professor Walter Beck for help in the management of this patient, the staff of the Cell Support Section, Department of Haematology, for their support, and the Unit for their dedicated nursing.

REFERENCES