Fetal marrow suppression after maternal chemotherapy for leukaemia

N A Murray, D Acolet, M Deane, J Price, I A G Roberts

Abstract

A preterm baby, whose mother received chemotherapy for acute leukaemia during pregnancy, required intensive care because of profound anaemia and neutropenia. Haemopoietic progenitor cell studies showed fetal marrow suppression. Those caring for such mothers and babies should know the possible serious effects chemotherapy for malignancies can have on a developing fetus. Long term follow up of the baby is imperative.

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Acute leukaemia in pregnancy is rare,¹ with few centres having extensive experience of caring for mother and fetus in this difficult situation. Ideally, management requires a team approach involving obstetricians, haematologists, and neonatal paediatricians. Cytotoxic drugs have theoretical risks of teratogenesis if administered to pregnant women in the first trimester, but in practice this risk has been shown to be small.² It seems likely, therefore, that this will encourage women receiving chemotherapy, even during the early stages of pregnancy, not to undergo therapeutic abortion. This, coupled with a good chance of achieving remission of acute leukaemia, means that it is important that possible major fetal complications of such treatment are made known.

Case report

A 36 year old pregnant woman presented at 25 weeks of gestation, complaining of tiredness, sore gums, and easy bruising. A full blood count showed anaemia and thrombocytopenia, and bone marrow examination confirmed acute myeloid leukaemia. She began chemotherapy with cytosine arabinoside (1 g/m²/day D1–3), daunorubicin (45 mg/m²/day D1–3), and etoposide (400 mg/m²/day D8–10), achieving remission by 30 weeks. Serial ultrasound scanning showed

no fetal abnormalities, but no fetal growth was seen from 30–32 weeks. At 32 weeks she also experienced no fetal movements for one day, with cardiotocography showing unprovoked fetal heart rate decelerations, suggesting fetal distress. The woman had completed her second course of chemotherapy 11 days before and was clinically well with rising blood counts (haemoglobin of 114 g/l, a white cell count of $2.0 \times 10^9/l$ (neutrophils $0.8 \times 10^9/l$), and a platelet count of $117 \times 10^9/l$). She therefore proceeded to have an emergency caesarean section. A live girl was delivered, who was immediately noted to be very pale and required active resuscitation. Birth weight was 1460 g (10th centile). Cord blood count confirmed anaemia and also demonstrated leucopenia with profound neutropenia (haemoglobin of 60 g/l (reticulocytes 1.3%), a white cell count of $2.0 \times 10^9/l$ (neutrophils 1%), and a platelet count of $290 \times 10^9/l$). She required ventilation for 10 hours while the anaemia was corrected by transfusion of packed cells. At 30 hours she developed a fever and because of persisting neutropenia (white cell count of $2.2 \times 10^9/l$ – neutrophils 1%) and developing thrombocytopenia (platelet count of $129 \times 10^9/l$) was given two doses of granulocyte colony stimulating factor (G-CSF) 10 µg/kg subcutaneously. Screening for septicemia showed no infection and the haematological abnormalities resolved by day 4. A cerebral ultrasound scan was normal and the rest of her neonatal course was uneventful. Erythropoietin was given for anaemia of prematurity, but at current follow up (one year) she remains well, is off all treatment, and has normal peripheral blood counts. Following delivery the woman completed her chemotherapy and has now received an autologous bone marrow transplantation.

CIRCULATING HAEMOPOIETIC PROGENITOR CELLS

The baby's bone marrow activity was assessed by assaying circulating haemopoietic progenitor cells at birth, and on days 5, 12, and 33. (Circulating progenitors reflect bone marrow progenitors and hence indirectly bone marrow activity.³) The progenitors assayed were: CFU-GM, which are the precursors of granulocytes/monocytes; BFU-e, the precursors of erythroid cells; BFU-MK and CFU-MK, the earliest precursors of megakaryocytes; and megakaryoblasts (mega-b), which give rise to megakaryocytes. Results are summarised in the table.

Department of
Haematology
I A G Roberts

Department of
Neonatal Medicine,
Royal Postgraduate
Medical School,
Hammersmith
Hospital, London
N A Murray

Department of
Paediatrics
D Acolet

Department of
Haematology
M Deane

Department of
Obstetrics, Hillingdon
Hospital, Uxbridge,
Middlesex
J Price

Correspondence to:
Dr Neil A Murray,
Department of Haematology,
Royal Postgraduate Medical
School, Hammersmith
Hospital, Du Cane Road,
London W12 0NN.

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Circulating haemopoietic progenitors

Day	Number of colonies/ml				Liquid culture cells/ml ($\times 10^3$)	
	CFU-GM	BFU-e	BFU-MK	CFU-MK	*Mega-b	†Mega
Birth	697	1376	ND	ND	44.9	7.92
5	1904	3024	ND	ND	176.9	31.6
12	ND	ND	241	2648	293.5	15.5
33	961	1663	226	1939	193.8	21.5
<i>Laboratory range:</i>						
Gestational age						
28–32 weeks	950–1475	1225–1775	128–946	1045–6009	51.3–494.6	9.2–46.4

*Mega-b=megakaryoblasts; †Mega=megakaryocytes; ND – not done.

Discussion

Although a number of centres have described their experience of cytotoxic chemotherapy in pregnancy,²⁻⁴ there is very little information in these reports about the haematological status of the babies. We know of only one previous case report in which the blood count changes were documented.⁵ (The baby had isolated neutropenia and the baby's bone marrow status was not assessed.)

In this case the baby developed pancytopenia within 30 hours, and circulating haemopoietic progenitor cell studies confirmed marrow suppression: CFU-GM were reduced at birth, consistent with the severe neutropenia. They increased to above normal levels by day 5. While this may have been due to the administration of G-CSF, it is more likely to have been the result of a rebound phenomenon as occurs in adults after chemotherapy. BFU-e were towards the lower end of our normal range at birth but doubled in the first five days of life. This contrasts with the usual pattern in which the number of BFU-e is highest in the first 24 hours of life and falls during the following week. At birth numbers of cultured megakaryoblasts and megakaryocytes were severely reduced. We have found that this predicts the development of thrombocytopenia during the first week of life.⁶ All progenitor markers had returned to normal by day 33.

We believe this is the first neonatal case of its kind to be investigated by serial study of the three main types of haemopoietic progenitor. The data show that the baby's marrow was actively regenerating after an acute insult. In this instance cytotoxic chemotherapy given to the mother caused fetal marrow suppression, roughly equal to the extent seen in the mother. This may have been due to the use of etoposide in this case, a relatively new antineoplastic agent which crosses the placenta and is particularly myelosuppressive. It is also highly

mutagenic,⁷ raising the possibility of late treatment induced leukaemia in this baby.

This case illustrates that severe fetal marrow suppression may occur if women receive full dose cytotoxic chemotherapy during pregnancy. Any decision to expedite delivery in this situation should take into account the possible haematological status of the fetus (which, if appropriate, could be assessed by cordocentesis). At birth the baby may have severe haematological abnormalities, require immediate resuscitation, and ongoing neonatal intensive care. After the neonatal period repeated follow up of the baby is essential, in view of the possible long term effects of cytotoxic agents.

All obstetricians, haematologists, and neonatal paediatricians involved in the care of such pregnant women should be aware of the potential risks to the fetus, ensure that delivery and neonatal care take place in an appropriate setting, and subsequently plan careful long term follow up of the baby.

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Poor prognosis after prolonged ventilation for bronchopulmonary dysplasia

Mary Wheeler, Janet M Rennie

Abstract

Of 47 babies mechanically ventilated for more than 27 days for bronchopulmonary dysplasia 20 eventually died. There were no neurodevelopmentally intact survivors among those who were ventilated for more than 50 days. Days of ventilation more powerfully predicted outcome than ultrasound evidence of brain injury.

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Prolonged neonatal mechanical ventilation is an indicator of poor prognosis, but there are

few estimates of the likelihood of normal survival. Overstreet *et al* studied 144 infants requiring more than 30 days' mechanical ventilation.¹ Survival to discharge was related to duration of ventilation, with 90% mortality for babies ventilated for more than 120 days. Long term survival and neurodevelopmental outcome were not reported.

Ventilation for more than 21 days was a powerful predictor of developmental delay at 18 months in infants with birth weights below 1201 g.² Luchi *et al* detected no relationship between duration of mechanical ventilation and neurodevelopmental outcome among 27

Neonatal Intensive Care Unit, Rosie Maternity Hospital, Robinson Way, Cambridge CB2 2SW
M Wheeler
J M Rennie

Correspondence to:
Dr Rennie.

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