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Short communication

Third trimester chemotherapy and neonatal hematopoiesis

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Summary. An 18-year-old woman with severe pancytopenia secondary to chemotherapy given in the third trimester of pregnancy and who delivered an infant with normal peripheral blood counts is reported. The literature is reviewed, and recommendations for the method of delivery in this setting are discussed.

Introduction

The potential toxicities of chemotherapeutic agents to the fetus are not well known, as experience with cytotoxic chemotherapy in pregnancy is limited. We now report the delivery of a male infant with normal blood counts despite profound simultaneous maternal leukopenia and thrombocytopenia following the administration of chemotherapy for metastatic Ewing's sarcoma.

Case report

An 16-year-old Mexican American woman presented at 5 months of gestation with painful swelling of the left lower extremity. Physical examination revealed a tender 10 cm × 3 cm mass over the left fibula. Biopsy was consistent with Ewing's sarcoma. Additional workup confirmed the presence of multiple small pulmonary metastases. Chemotherapy was initiated with cyclophosphamide, methotrexate, adriamycin, and vincristine. The patient tolerated the first two cycles of therapy with moderate cytopenias necessitating transfusion of red blood cells and platelets, but without requiring hospitalization. On days 43–45 of treatment the patient received cyclophosphamide 1200 mg/m^2, methotrexate 12 mg/m^2 daily for 2 days, and adriamycin 20 mg/m^2 daily for 3 consecutive days; 12 days later she developed severe mucositis and fever to 39 °C and was admitted to hospital with a white blood cell count of 200/mm^3, hemoglobin 9 g %, and platelet count 30000/mm^3. The patient was treated with antibiotics i.v. and 6 h after admission, at approximately 7 months of gestation, experienced spontaneous rupture of membranes and went into active labor. She was given 10 units of platelets, 1 unit of packed red blood cells and underwent an uncomplicated caesarean section with delivery of a 2200-g healthy male infant. The baby's initial blood counts, obtained 30 min after birth, revealed a white blood cell count of 7200/mm^3 with 28% PMNs, 69% lymphocytes, 2% monocytes, 1% eosinophils, 15 nucleated red blood cells per 100 WBCs and a platelet count of 151000/mm^3. The infant was discharged after 3 days and at 10 weeks continues to enjoy normal growth and development. The mother has had regression of pulmonary metastases and continues to receive aggressive therapy.

Discussion

To our knowledge this is the fourth reported case in which neonatal blood counts have been recorded at delivery in a baby whose mother was pancytopenic as a result of cytotoxic chemotherapy. In the cases reported by Doney et al. [3], Dietz and Gee [1], and Nordlund et al. [7] normal blood counts were also found despite marked maternal pancytopenia (Table 1). In Doney et al.'s case, the maternal bone marrow was hypoplastic 4 weeks after chemotherapy for acute myelogenous leukemia, whereas in the case reported by Dietz and Gee the etiology of pancytopenia was not specified and might have been due either to chemotherapy or persistent leukemia. Although we did not perform a bone marrow study on our patient, there was no evidence of bone marrow compromise prior to chemotherapy.

The normal fetal blood counts despite maternal pancytopenia raises the question of transplacental passage of chemotherapeutic agents and its impact on fetal hematopoiesis [9]. There is a paucity of data on this subject. However, detectable levels of cyclophosphamide but not of adriamycin have been found in amniotic fluid after maternal exposure to these drugs in single case reports [2, 5]. Our patient received both these agents in significant doses. D'Incalci et al. reported an amniotic fluid level approximately 25% that of maternal plasma 1 h after the administration of 400 mg/m^2 cyclophosphamide for the treatment of advanced Hodgkin's disease during the third trimester of pregnancy [2]. The extent of fetal hepatic conversion of cyclophosphamide to its active form is unknown, but it has been reported that fetal liver possesses the P-450 monooxygenase microsomal enzymes required for conversion of cyclophosphamide to its cytotoxic metabolites [10]. Pharmacologic data on transplacental passage of methotrexate and vinca alkaloids are also limited. Since methotrexate is known to be teratogenic in humans and vinca alkaloids, in rats, these agents must cross the placental barrier [4, 11]. The extent of their transplacental passage and subsequent

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Table 1. Summary of data relating to birth of babies to pancytopenic mothers

Chemotherapy	Diagnosis	Interval from chemotherapy to delivery	Maternal blood counts	Newborn blood counts	Method of delivery	Outcome	References
Cyclophosphamide Adriamycin Methotrexate Vincristine	Ewing's sarcoma	12 days 39 days	WBC 200/mm^3 Hemoglobin 9 g% Platelets 30 000/mm^3	WBC 7200/mm^2 (PMNs 2016) Hemoglobin 18 g% Platelets 151 000/mm^3	Caesarean section	Apgar 9[5] Normal growth and development at 2 months Maternal recovery	Current report
Hydroxyurea Daunorubicin Cytosine arabinoside Vincristine 6-Thioguanine Prednisone	Acute leukemia	>4 weeks	WBC 100/mm^3 Hematocrit 29 Platelets 19 000/mm^3 (transfused)	WBC 6200/mm^3 (PMNs 3200) Hematocrit 35 Platelets 400 000/mm^3	Vaginal	Apgar 8[5] Maternal death postpartum due to sepsis	Doney et al. [3]
Prednisone Daunorubicin Cytosine arabinoside 6-Thioguanine	Acute leukemia	7 days	WBC 200/mm^3 Hemoglobin 11 g% Platelets 58 000/mm^3 (transfused)	normal	Vaginal	Apgar 10[5]	Dietz and Gee [1]
Vinblastine	Hodgkin's disease	7 days	WBC 700/mm^3	WBC 11 000/mm^3 (PMNs 5110) Hemoglobin 17.2 g% Platelets 315 000/mm^3	Vaginal	"Normal infant" Maternal recovery	Nordlund et al. [7]

impact on fetal hematopoiesis is unknown. Although our patient received vincristine, this drug is minimally marrow-suppressive, and it was administered 39 days before delivery. In this connection, Nordlund et al. reported a pregnant patient with severe bone marrow suppression from velban chemotherapy for Hodgkin's disease who delivered an infant with normal peripheral blood counts [7]. Our observation, taken together with the others cited, implies greater fetal than maternal bone marrow reserve. However, in 1979 Okun et al. reported an 18-year-old woman with acute leukemia, who was maintained on 6-mercaptopurine until 3.5 weeks before delivery. At delivery, the mother had a normal CBC but the baby was pancytopenic with a hypocellular bone marrow [8]. On the other hand, McConnell and Bhoola described a baby with mild anemia and normal platelet count born to a leukemic mother maintained on 6-mercaptopurine from conception until delivery. The WBC in this case was not specified [6].

We recommended caesarean section for the delivery of our patient's baby because of the fear of neonatal thrombocytopenia and subsequent birth trauma. However, this fear was unfounded, since the baby's blood counts were normal [7]. Prematurity and breech presentation were further indications for caesarean section, however. In future, the method of delivery relative to fetal blood counts might be decided after examination of fetal scalp blood. For maternal welfare, thrombocytopenia can be managed by platelet transfusion, but leukopenia poses a more difficult management decision. Caesarean section has the advantage of providing a more sterile approach, though a tissue plane in addition to the placental site is exposed, whereas vaginal delivery is a contaminated procedure. Until further experience is available relative to neonatal and maternal blood counts in these circumstances, management should be individualized when markedly pancytopenic mothers are to be delivered of potentially leukopenic and/or thrombocytopenic infants.

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