Administration of Cyclophosphamide During Late Pregnancy and Early Lactation: A Case Report

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Burkitt lymphoma was diagnosed in a patient during the third trimester of pregnancy. Treatment with a low-dose, seven-day course of intravenous cyclophosphamide gave a good response which permitted the pregnancy to be carried to term, with delivery of a normal infant. When the mother received cyclophosphamide during lactation while the baby was breast-fed, the infant's leukocyte and platelet counts were rapidly depressed. Results in this patient and a survey of reported cases in which cyclophosphamide was administered during pregnancy and lactation lead to the conclusions that (1) low-dose intravenous cyclophosphamide therapy is not hazardous to the fetus during late pregnancy; (2) mammary concentration of the drug is too toxic to the infant's bone marrow; and (3) breast-feeding the baby should be suspended during the period the mother is receiving cyclophosphamide treatment.

Cyclophosphamide (Endoxan), an effective alkylating agent, has found wide use in treating Burkitt lymphoma and other tumors, such as breast cancer. Occasionally its use is necessary during pregnancy or lactation. Therefore, it is important to assess the risks to which the fetus or infant is subjected under these circumstances.

Many lactating women have been referred to the Oncology Unit with malignant tumors already in advanced stages, eg breast tumor, Burkitt lymphoma, etc. The referring physicians usually state that the tumor was discovered a few months previously, when the patient was in the third trimester of pregnancy and, because she did not want to lose the pregnancy, she was advised to wait until after delivery when she could be given cytotoxic drugs. This experience prompted the author to review the literature for information about the safety of administering cytotoxic drugs (particularly cyclophosphamide, which is the only drug readily available to us) to patients during the third trimester of pregnancy. It was on the strength of this review that the Burkitt lymphoma patient reported here was treated.

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Review of the Literature

Lacher and Geller[1] used cyclophosphamide during the second half of pregnancy with no harm to the fetus. Hardin[2] used a high-dose intermittent regimen of the drug during the third trimester of pregnancy without complications to the fetus, and with normal leukocyte counts of 17,000/mm^3 and a hematocrit level of 62 percent cord blood. Bounameaux and Durenne[3] treated a lactating patient with busulphan, another alkylating agent. Although the maternal white blood count was depressed, there was no significant change in the baby's blood. However, no estimation was made of the busulphan content in the milk. To this author's knowledge, there has been no report of treating a lactating (nursing) patient with cyclophosphamide.

The present report is of a patient with Burkitt lymphoma who was successfully treated with a single course of low-dose cyclophosphamide during the third trimester of pregnancy. She delivered a normal baby. But when she was retreated with cyclophosphamide, because of recurrence of her tumor while she breast-fed her three-week-old baby, the infant's leukocyte and platelet counts were rapidly depressed.

Case History

The mother was an 18-year-old school girl, primigravida, who was referred to the University College Hospital for evaluation of swelling of the sternum. She was pregnant and in 26th week of gestation. Histopathology of the biopsy tissue from the mass revealed the presence of macrophages with surrounding clear areas, giving the typical "starry-sky" appearance, and a diagnosis of Burkitt lymphoma was confirmed by phase-contrast cytology.

One course of low-dose cyclophosphamide was given at 10 mg/kg intravenously once daily for seven days, for a total of 3.5 gm. The treatment was well tolerated except for uterine contractions (false labor) on the fourth day of treatment, and leukopenia; the leukocyte count fell to 1,500/mm^3. The sternal mass virtually disappeared at the end of this first course of treatment.

Three days after the last dose of cyclophosphamide, the patient ran a two-day high fever of 103 F. There were very strong uterine contractions and the cervix was one-finger dilated. She was transferred to the Labor Ward where she was observed for four days. The uterine contractions stopped and she was kept in the hospital for two weeks during which period her leukocyte count returned to its pre-treatment count of 3,600/mm^3. She went into labor at a local hospital, six weeks after the last dose of cyclophosphamide, and delivered a 2,160 gm (4lb, 12oz) normal male infant.

When the patient returned to UCH three weeks after delivery, the tumor had recurred and grew very rapidly, involving both breasts and presenting with large palpable masses. The patient was dyspenic. Her leukocyte count

Table 1. Hemograms for Mother and Baby During Treatment (Mother) with Cyclophosphamide

	Mother's Record			Baby's Record		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Hemoglobin (gm/100 cc)	9.6	10.4	10.7	15.2	15.5	13.8
Hematocrit (percent)	30	35	31	49	50	40
Leukocytes count (per mm^3)	4,400	3,100	3,000	4,800	4,600	3,200
Platelet count (per mm^3)	280,000	—	270,000	270,000	—	47,000
Differential counts:						
Neutrophils (percent)	60	—	70	14	—	40
Lymphocytes (percent)	35	—	25	76	—	53
Monocytes (percent)	3	—	2	7	—	6
Eosinophils (percent)	2	—	3	2	—	1
Basophils (percent)	0	—	0	1	—	0

—test not done

was 4,400/mm^3; platelet count was 270,000/mm^3. The patient, who could not be persuaded to stop breast-feeding her 20-day-old baby, was placed on a small dose of cyclophosphamide, 6 mg/kg (total 300 mg) intravenously daily. She died suddenly after the third dose of the drug. The 23-day-old baby, who was alive at the time of the mother's death, was taken away by some relatives and was lost to follow-up.

Because the baby was not delivered at UCH, there was no record of the hemogram of the cord blood. However, while the patient was breast-feeding her baby and receiving cyclophosphamide, daily hemograms were performed on her and the baby yielding the data recorded in Table 1.

Discussion

Several investigators[4-8] have reported leukopenia in healthy blacks. Akinyanju and Grossman[9] reported leukocyte counts in 175 healthy Nigerians, the mean total count was 5426/mm^3. Araba[10] also reported hematological variables in 600 healthy Nigerians, the leukocyte count also ranged from 2,000 to 8,000/mm^3. Durodola[11] reported the pattern of leukocyte counts in untreated Burkitt lymphoma patients in Ibadan.

In our patient, the usual normal counts ranged between 3,000 and 4,500/mm^3; the highest leukocyte count recorded for her while she was hospitalized was 5850/mm^3. Her leukocyte count of 4,400/mm^3 on day 1 was prior to the first dose of cyclophosphamide (Table 1). The 23-day-old baby's first leukocyte count of 4,800/mm^3 was definitely low for his age, however, the drop from 4,800/mm^3 to 3,200/mm^3 in three days was a sign of toxicity. The platelet count dropped from 270,000/mm^3 to 47,000/mm^3 in three days.

It is doubtful that the transplacental concentration gradients of the drug were very toxic to the fetus, but the mammary concentration of the drug was definitely toxic to the infant bone marrow. In most of our patients with Burkitt lymphoma (mostly children) cyclophosphamide did not rapidly or drastically depress the platelet count, but in this infant the platelet count was depressed while the mother's platelet count was unaffected.

The problem of breast-feeding the baby is perhaps peculiar to the developing countries where artificial feeding is rather too expensive for some families and a taboo to others. The need is clear for further studies concerning placental transfer of cyclophosphamide to the fetus and mammary transfer of the drug to the nursing infant. Criteria must be sought for treatment regimens which afford the greatest fetal/infant safety at specific times during pregnancy and lactation. From the author's observation it appears that breast-feeding should be suspended during the period the mother is receiving cyclophosphamide treatment.

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