Incidence of Neonatal Neutropenia and Leukopenia After In Utero Exposure to Chemotherapy for Maternal Cancer

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Objective: The main purpose of this article was to report the incidence of neonatal neutropenia or leukopenia after chemotherapy exposure during pregnancy according to the time elapsed between treatment during pregnancy and birth.

Background: A single study reports 33% of infants exposed to chemotherapy within the last month of pregnancy are born with neutropenia, which can place the newborn at risk for nosocomial infections. On the basis of this report, chemotherapy is typically stopped by 34 weeks of pregnancy to avoid maternal or neonatal myelosuppression at delivery. Such a pause in treatment may affect maternal health. Determining the true incidence of neutropenia after chemotherapy in relation to the time of this lapse in treatment is important to support this practice.

Materials and Methods: Complete blood counts are collected for newborn whose mothers were treated for cancer during pregnancy and enrolled in the Cancer and Pregnancy Registry. Neutropenia was defined as absolute neutrophil count < 1000 mm3 and leukopenia was defined as white blood cells < 5000 cells/μL. Incidence of neutropenia was calculated according to the time elapsed from last chemotherapy treatment until birth. Fisher's exact test is used to determine if neutropenia or leukopenia is related to the time elapsed between chemotherapy during pregnancy and newborn birth. A Bayesian analysis evaluated the occurrence of neutropenia and leukopenia according to the number of days between the initiation of chemotherapy and birth.

Results: A total of 135 infants exposed to chemotherapy in utero with a complete blood count collected at birth were identified from the database. Only 7.3% and 2.9% of infants were born with neutropenia or leukopenia, respectively. The highest incidence of newborn neutropenia occurred in infants delivered 22 to 28 days after chemotherapy.

Conclusions: The incidence of neutropenia peaks when chemotherapy is given 22 to 28 days before birth, while leukopenia is highest if delivery is < 7 days from chemotherapy.

Key Words: cancer, chemotherapy, neutropenia, pregnancy

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Approximately 1 in 1000 pregnancies are complicated by cancer.[1] As maternal age at first pregnancy increases, the incidence of age-dependent malignancies may increase. The most common malignancies include breast cancer, cervical cancer, leukemia, and melanoma.[2] Cancer management in pregnancy must balance the maternal benefit with the fetal risk. Many studies do show that most cytotoxic drugs can be safely administered to pregnant patients who need chemotherapy after the first trimester.[3–7] Organogenesis is completed between the tenth to twelveth week of gestation, and, thus, chemotherapy administered after this time period will not cause major organ damage to the fetus.[8] Developmental studies in children exposed to chemotherapy show comparable performance when compared with unexposed controls.[9–11]

Recommendations from obstetricians and oncologists with regard to when pregnant women undergoing chemotherapy should stop their treatment before delivery are based on a case series reported by Reynoso et al.[12] In this report, one-third of newborns delivered within 1 month of chemotherapy exposure in utero were born with neutropenia. Pausing chemotherapy by the thirty-fifth week of gestation is the current practice. The purpose of this pause in therapy is to avoid delivery during the maternal nadir period, to allow placental excretion of maternal medication, and to modify the risk of neonatal myelosuppression. During the transient myelosuppression, the infant may be susceptible to infections in the hospital.[13] Two neonatal deaths that occurred after in utero exposure are reported in the literature.[14,15]

Neutropenia can be secondary to decreased neutrophil production, increased neutrophil destruction, or a combination of both. Neutropenia occurs most often in association with prematurity, maternal hypertension, sepsis, twin-to-twin transfusion, alloimmunization, and hemolytic disease. It can be associated with many chemotherapeutic agents used in cancer treatment.[10] Absolute neutrophil counts (ANC) below 1000/μL are seen in ~6% to 8% of all neonatal intensive care unit (NICU) admissions; of these, the majority occur in the preterm infant.[13] The ANC is not measured directly. It is derived by multiplying the white blood cell count (WBC) count times the percent of neutrophils in the differential WBC count. The percent of neutrophils consists of the segmented (fully mature) neutrophils+the bands (almost mature neutrophils). In this current study, 9 of 122, or 7.3% of infants experienced a transient myelosuppression.

In this study, we will examine cord blood or newborn complete blood count (CBC) with differentials in relation to time (in days) from final chemotherapy exposure during pregnancy, to the day of birth.

MATERIALS AND METHODS

The Cancer and Childbirth Registry is a cohort of pregnancy women diagnosed with cancer who enrolled voluntarily into a single database. Creation of the Registry was approved by the Institutional Review Board of Cooper Medical School at Rowan University. Women provide written consent to have cancer and delivery information, including health of the newborn, collected from their treating physicians. Enrollment is voluntary and does not affect the patient's treatment plan. To avoid bias, enrollment is made at time of cancer diagnosis and before the outcome of the pregnancy is known. This study is a retrospective review of newborn CBC and differentials and

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ANCs on the day of birth after chemotherapy exposure in utero. A total of 135 infants exposed to chemotherapy in utero with a CBC collected at birth were identified from the database from 8/1/1995 to 12/01/2017. Blood was drawn either from the infant or sent from the umbilical cord. If a differential was not available, WBC was used to determine the incidence of leukopenia. Neutropenia was defined as ANC $< 1000\,mm^3$ and leukopenia was defined as WBC <5000 cells/μL. Despite the recommendation to send neonatal CBC from the cord blood at delivery or neonatal peripheral blood in all cases of chemotherapy during pregnancy, this was not performed in all cases. Excluded from the study were neonates exposed to chemotherapy who did not have any CBC on file during the first 24 hours of life.

For this study, the following 5 analyses were completed: (1) What was the rate of neutropenia or leukopenia in babies delivered at various times (in days) between last chemotherapy during pregnancy and delivery?, (2) Of babies who were neutropenic or leukopenic at birth, what was the rate of bacteremic infection requiring antibiotics in the nursery?, (3) Did the type of chemotherapy regimen or interval of administration affect the rate of neutropenia or leukopenia?, (4) When controlling for preterm births (gestational age defined as less than or equal to 36.9 wk), was the incidence rate of neutropenia or leukopenia significant at any particular time from between the last treatment in pregnancy to delivery?, and (5) Were the rates of neutropenia or leukopenia affected by maternal use of pelfilgrastim?

A Bayesian analysis was performed to determine predicted rates of neutropenia and leukopenia according to the time between chemotherapy exposure and birth. This method estimated the probability of the outcome at different time points beginning when the mother discontinued chemotherapy.

RESULTS

A total of 135 mother-infant pairs with CBC available from the Cancer and Childbirth Registry were included in the study. In 13 cases, the full differential was not provided, so a calculated ANC was only available for 122 mother infant pairs. The newborns were born to mothers who had different cancers treated with different chemotherapy regimens. The cancers included breast, acute or chronic leukemia, bladder, cervical, colon, Hodgkin's or non-Hodgkin's lymphoma, ovarian, rectal, stomach, or tongue cancer, along with sarcoma. The most common cancers were breast and Hodgkin's lymphoma.

TABLE 1. Cancer Diagnosis, Chemotherapy Regimen, and Interval of Treatment

Diagnosis	N	Regimen	Interval	No. Cycles
ALL	1	Intrathecal methotrexate, vincristine, daunorubicin	1	6
ALL	1	Cytoxan/ara-C/6MP/vincristine/L-asparagenase/intrathecal methotrexate, cytoxan, and daunorbubicin	4	2
AML	1	ATRA, daunorubicin	Daily	1
Bladder	1	Gemcitabine/cisplatin	3	3
Breast	56	Doxorubicin/cyclophosphamide	2-3	1-8
Breast	13	Doxorubicin/cyclophosphamide; paclitaxel	1-3*	1-15
Breast	3	Doxorubicin/cyclophosphamide; docetaxel	1-3*	8-10
Breast	1	Doxorubicin/cyclophosphamide; paclitaxel; docetaxel	2-3*	9
Breast	1	Doxorubicin/cyclophosphamide; carboplatin/paclitaxel	1-2*	8
Breast	1	Doxorubicin/cyclophosphamide; cyclophosphamide/docetaxel	3	4
Breast	1	Epirubicin/cyclophosphamide	2-4	6-7
Breast	1	Epirubicin/cyclophosphamide; paclitaxel	2	7
Breast	14	FAC	3-4	4-8
Breast	1	5-fluorouracil /cyclophosphamide	4	4
Breast	1	Doxorubicin/cyclophosphamide; epirubicin/cytoxan; paclitaxel	2	8
Breast	2	Paclitaxel	1	6-12
Cervical	2	Cisplatin/taxol	3	3-4
Cervical	1	Carboplatin/paclitaxel	3	2
Cervical	1	Vincristine/cisplatin	3	4
CML	1	Hydroxyurea	2	2
Colon	3	Folfox	2	4-9
Hodgkin's lymphoma	10	ABVD	2-4	2-10
Hodgkin's lymphoma	1	Gemcitabine/oxaliplatin	3	2
Non-Hodgkin's lymphoma	4	CHOP/rituxan	3	2-6
Non-Hodgkin's lymphoma	1	CHOP	3	2
Non-Hodgkin's lymphoma	1	RICE	NA	1
Non-Hodgkin's lymphoma	1	EPOC	3	2
Ovarian	1	Oxaliplatin	3	3
Ovarian	1	BEP	3	3
Ovarian	1	Carboplatin	3	5
Ovarian	1	Cisplatin/taxotere	3	2
Sarcoma	1	Cytoxan/adriamycin/vincristine	2	3
Stomach	1	Folfox	2	6
Tongue	1	Cisplatin	1	7

Number of cycles: neutropenia, $P = 0.29$; leukopenia, $P = 0.45$.
Interval of first regimen: neutropenia $P = 75$; interval of second regimen: neutropenia $P = 1.0$.
Interval of first regimen: leukopenia $P = 1.0$; interval of second regimen: leukopenia NA too few patients.
*Reflects interval of first regimen only.
ABVD indicates doxorubicin/bleomycin/oncovin/dacarbazine; BEP, bleomycin/etoposide/cisplatin; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisolone; EPOC, etoposide/prednisone/vincristine/cyclophosphamide; folfox, oxaliplatin/5-FU/leucovorin; NA, not available; RICE, rituximab/ifosfamide/carboplatin/etoposide.

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TABLE 2. Neutropenia and Leukopenia According to Chemotherapy Regimen in Pregnancy

Regimen	Incidence Neutropenia (N = 9/122) (n/N [%])	*P*	Incidence Leucopenia (N = 4/135) (n/N [%])	*P*
Doxorubicin/cyclophosphamide	6/50 (12)		2/56 (3.6)	
Doxorubicin/cyclophosphamide/paclitaxel	1/14 (7.1)		0	
FAC	0		0	
ABVD	0		0	
RCHOP	1/14 (7.1)		1/14 (7)	
Other	1/27 (0.8)		1/31 (3.2)	
		0.72		0.84
With neulasta	1/24 (4.2)		1/26 (3.8)	
Without neulasta	8/98 (8.2)	0.69	3/109 (2.7)	0.58

ABVD indicates doxorubicin/bleomycin/oncovin/dacarbazine; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisolone.

The most common chemotherapy regimens were doxorubicin/cyclophosphamide, 5-fluorouracil/doxorubicin/cyclophosphamide, or epirubicin/cyclophosphamide, with or without paclitaxel or docetaxel for breast cancer and doxorubicin/bleomycin/vincristine/dacarbazine (ABVD) for Hodgkin's lymphoma. Other less commonly used regimens include daunorubicin, gemcitabine/cisplatin, intrathecal methotrexate/vincristine/daunorubicin, cyclophosphamide/Ara-6/6-MP/vincristine/L-asparagenase/cisplatin/paclitaxel; cisplatin/vincristine, carboplatin/paclitaxel, hydroxyurea, oxaliplatin/5-fluorouracil/leucovorin (FOLFOX), gemcitabine/oxaliplatin, rituximab/ifosfamide/carboplatin/etoposide (RICE), cyclophosphamide/doxorubicin/vincristine/prednisolone (CHOP) with or without Rituximab; etoposide/prednisolone/vincristine/cyclophospohamide/hydroxydaunorubicin: doxorubicin (EPOCH) or bleomycin/etoposide/cisplatin (BEP).

The less commonly used regimens were grouped together as "other" in our analysis. See Table 1 for cancer types, chemotherapy regimens, intervals, and number of cycles. The incidence of suspected sepsis or use of antibiotics in the NICU was not statistically different between the infants with or without neutropenia or leukopenia. Raw data rate of neonatal neutropenia after doxorubicin/cyclophosphamide was 12%, after doxorubicin/cyclophosphamide+paclitaxel or RCHOP was 7.1%, and 0% after 5-fluorouracil/doxorubicin/cyclophosphamide or ABVD but rates according to chemotherapy regimen were not significantly different, $P = 0.72$ (Table 2). There was also no difference in incidence of leukopenia by regimen, $P = 0.84$. The incidence of neutropenia and or leukopenia analyzed according to the interval at which chemotherapy was given in weeks between courses was not statistically significant.

TABLE 3. Neutropenia and Leukopenia According to Time Elapsed Between Delivery and Last Chemo in Pregnancy

Last treatment to Delivery (d)	N	Incidence Neutropenia (n/N [%])	N	Incidence Leukopenia (n/N [%])
< 7	9	1 (11)	9	1 (11)
8-14	18	0	19	1 (5.3)
15-21	26	2 (7.7)	28	0
22-28	15	3 (20)	19	1 (5.3)
> 29	54	3 (5.5)	60	1 (1.7)

Neutropenia defined as absolute neutrophil count (ANC) < 1000.
Leukopenia defined as white blood cell < 5000.
Time to delivery neutropenia ($P = 0.20$).
Time to delivery leukopenia ($P = 0.17$).

There appeared to be a lower incidence of neutropenia after maternal filgrastim or pegfilgrastim, but this was not significant (without filgrastim or pegfilgrastim, neutropenia 8.2%; with filgrastim or pegfilgrastim 4.2%, $P = 0.69$).

The mean gestational age at birth for this cohort was 35.8 (SD ± 2.9) weeks. The overall rate of neutropenia was 9 of 122, 7.4% (95% confidence interval [CI], 3.6-23.9). The highest risk for neutropenia was at interval 22 to 28 days after chemotherapy, 3 of 15, 20% (95% CI, 5.3-48.6). For other time periods, the rate was as follows: <7 days: 1 of 9, 11% (95% CI, 0.58-49.3), 8 to 14 days: 0 of 18, 0% (95% CI, 0.51-21.8), 15 to 21 days: 2 of 26, 7.7% (95% CI, 1.3-26.6), and > 29 days between last chemotherapy during pregnancy and delivery: 3 of 54, 5.6% (95% CI 1.5-16.3) (Table 3). In the 9 newborns with neutropenia, the mean gestational age at birth was 34.2 weeks (SD ± 3.8), and 8 of 9 were preterm. Only 1 infant with neutropenia was born after 37 weeks.

Overall, 4/135, or 3.0% (95% CI, 1.5-16.3) of newborns were born with WBC < 5000 cells/μL (leukopenia). The rates of leukopenia were as follows: highest during the first week (ie, <7 d): 1 of 9, 11.1% (95% CI, 0.6-49.3), 8 to 14 days: 1 of 19, 5.3% (95% CI, 0.3-28.1), 15 of 21 days: 0 of 28, 0% (95% CI, 0.3-15.0), 22 to 28 days: 1 of 19, 5.3% (95% CI, 0.3-28.1), and > 29 days between last chemotherapy during pregnancy and delivery: 1 of 60, 1.7% (95% CI, 0.1-10.1).

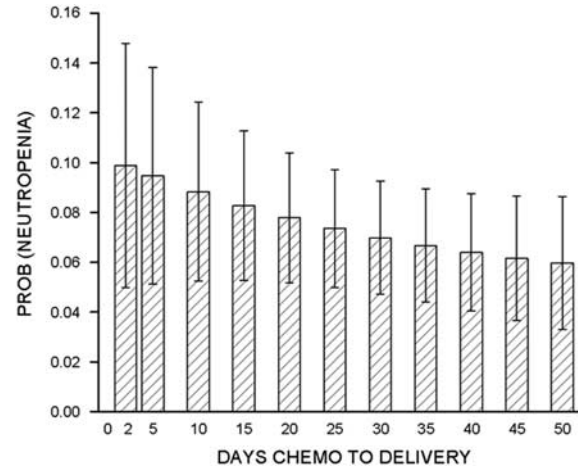

FIGURE 1. Bayesian analysis: probability of neutropenia according to time to delivery in days.

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The incidence of suspected sepsis or use of antibiotics in the NICU was not statistically different between the infants with or without neutropenia or leukopenia.

Because of the low incidence of neutropenia/leukopenia in this cohort, a Bayesian analysis evaluated the occurrence of neutropenia and leukopenia according to the number of days between the initiation of chemotherapy and birth (Fig. 1). The Bayesian approach allowed for the analysis of low incidence data providing estimates of the incidence for different choices of time from chemotherapy to time of delivery, along with 95% credible limits for the estimates. The probability of neutropenia gradually increases close to 10% the closer the final in utero dose of chemotherapy occurs to time of delivery. Similarly, the probability of leukopenia decreases the longer the length of time between chemotherapy in pregnancy and delivery. As premature infants have a higher risk for neutropenia,[13] results were adjusted for premature gestational age at birth. Leukopenia and neutropenia were not felt to be due to premature delivery (neutropenia: $P = 0.27$; leukopenia: $P = 0.30$).

DISCUSSION

This retrospective chart review shows that the incidence of neutropenia peaks when chemotherapy is given 22 to 28 days before birth, while leukopenia is highest if delivery is <7 days from chemotherapy. By Bayesian analysis, the longer the time period between the time of the last administration of chemotherapy and delivery, the lower the rate of neonatal neutropenia or leukopenia. In Reynoso and colleagues' publication of 49 cases of leukemia treated during pregnancy, 17% of the infants overall were born with transient neutropenia, and of those exposed within the last 4 weeks of pregnancy, 33% were born with transient neutropenia. One infant in this series died at 21 days of life from sepsis. In this review, only 7.3% and 2.9% of infants were born with neutropenia or leukopenia, respectively. Fifty percent, or 69 of 136 infants were treated within 28 days before delivery. The highest incidence of newborn neutropenia occurred in infants delivered 22 to 28 days after chemotherapy, clinically longer than the 7 to 14 days during which nonpregnant patients experience such a nadir after chemotherapy. A limitation of this study is that maternal blood indices were not available for correlation or comparison with newborn results.

Using Bayesian analysis, an estimation of the probability of neutropenia is calculated. The probability of neutropenia gradually increases to almost 10%, the closer the completion of chemotherapy is to delivery. Shown in Figure 1 are raw rates of newborn neutropenia or leukopenia that can be provided to oncologists, obstetricians, and patients so a decision can be made about timing of maternal treatment during pregnancy.

The chemotherapy regimen itself or the interval at which it was given did not affect rates of neutropenia or leukopenia. Although not significant, there was a trend towards a decreased incidence of neonatal neutropenia when mothers received filgrastim or pegfilgrastim in pregnancy.

In summary, similar to the paper by Reynoso, newborn neutropenia was highest when chemotherapy was given 3 to 4 weeks (22 to 28 d) before birth, but was still not statistically different than other time intervals analyzed. The longer the time period between in utero chemotherapy exposure and delivery, the lower the rate of either neutropenia or leukopenia in the newborn. Predicted rates can be provided to practitioners who are deciding what timing of treatment and delivery may be clinically best for the mother, balanced against neonatal risk. There was no significant influence of the type of chemotherapy given, the interval or the number of cycles during pregnancy.

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