Acute Leukemia during Pregnancy

A Report on 37 Patients and a Review of the Literature

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BACKGROUND. Acute leukemia (AL) requiring cytotoxic treatment occurring during pregnancy poses a very difficult therapeutic dilemma.

METHODS. By means of a mail questionnaire, information on a series of 37 patients with a diagnosis of AL during pregnancy was collected from 13 French centers between December 1988 and November 2003.

RESULTS. Thirty-one patients had acute myeloid leukemia (AML), and 6 patients had acute lymphoblastic leukemia (ALL). Nine patients were diagnosed during the first trimester, 10 patients were diagnosed during the second trimester, and 18 patients were diagnosed during the third trimester. Fifteen pregnancies ended with therapeutic or spontaneous abortion. There were 13 normal deliveries, including 1 gemellary pregnancy, and 9 Cesarean sections. Twenty-three healthy babies survived from the 37 pregnancies, of whom 15 babies had been exposed to chemotherapeutic agents. A complete remission was achieved in 34 patients. Eleven women had severe extrahematologic complications during the induction remission course. The median disease-free survival (DFS) was not reached, with a 5-year DFS of 54%. Ten patients developed recurrent disease. Overall, 12 of 37 pregnant women died from leukemia.

CONCLUSIONS. Pregnancy does not affect the course of AL. In the first trimester, termination of pregnancy should be discussed because of the potential fetal consequences of chemotherapy. Chemotherapy treatment during the second or third trimester may not require termination of pregnancy, because as remission of AL and delivery of a normal infant are likely to be obtained. ***Cancer* 2005;104: 110–7.** *© 2005 American Cancer Society.*

KEYWORDS: acute leukemia, pregnancy, chemotherapy, remission.

Although acute leukemia (AL) occurs mostly in older patients, it also may be seen in women of childbearing age. It is not surprising that, in some patients, the management of AL will be complicated by a coexistent pregnancy. However, the association of leukemia and pregnancy is uncommon. Its incidence is estimated to be 1 in 75,000 pregnancies.[1] There is no standard approach for this clinical dilemma, in part because of variables like the type of malignancy, the seriousness of the symptoms, and the patient's personal beliefs. In many patients, the diagnostic workup has to be altered because of the pregnancy; and, often, available treatments have varying risks to the fetus.[2,3] Although chemotherapy reportedly presents some risks during the first trimester, it is claimed that it can be administered safely during the second and the third trimesters.[4–6]

In the current study, we report on 37 patients with AL that occurred during pregnancy in 13 French centers over the past 15 years. We analyze their characteristics and outcomes, and we compare this group of patients with patients reported in the literature.

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MATERIALS AND METHODS

Patients

In this retrospective analysis, information was collected from 13 French center on patients with AL that occurred during pregnancy who were diagnosed between December 1988 and November 2003. To obtain patient information, questionnaires were sent to all participating centers. Only patients who were known to be pregnant when the diagnosis of AL was made were included. Patients with pregnancies that occurred during or after treatment for AL were excluded.

For patient inclusion, diagnostic evaluation and morphologic classification of AL were carried out as described previously using French–American–British criteria.[7,8] Cytogenetic data were available in 34 patients. For acute myeloid leukemia (AML), the Medical Research Council cytogenetic classification system was applied.[9] Favorable abnormalities included t(15; 17), t(8;21), and inv(16), irrespective of additional abnormalities. Cytogenetics were defined as adverse if they included ≥ 5 unrelated abnormalities (complex karyotype) or 1 of the following abnormalities: -5, del(5q), -7, abnormalities of 3q. An intermediate prognosis was assumed in the presence of either a normal karyotype or other chromosomal changes that were not encompassed in the favorable or adverse groups.

Obstetricians who were experienced with complicated pregnancies followed all patients throughout their pregnancies. Patients and families were kept fully informed. Treatment strategies were planned and carried out taking into consideration each family's decisions.

Treatment

Induction treatment of AML consisted of standard-dose or intermediate-dose cytarabine combined with an anthracycline (idarubicin, daunorubicin, rubidazone, or daunoxome), with or without etoposide. In patients with acute promyelocytic leukemia (APL), all-*trans* retinoic acid (ATRA) was associated with cytarabine and daunorubicin. Induction therapy for acute lymphoblastic leukemia (ALL) consisted of a standard, 4-week, 4-drug or 5-drug chemotherapy regimen of combined daunorubicin, cyclophosphamide, vincristine, and prednisone with or without L-asparaginase.

Statistical Analysis

Univariate analyses of associations between categorical factors were performed using the chi-square test. For continuously distributed variables other than event times, differences between groups also were tested using the Wilcoxon rank-sum test. The 95% confidence intervals (95%CIs) of the complete remission (CR) value were calculated using the exact binomial formula. Overall survival (OS) and disease-free survival (DFS) curves were estimated by the Kaplan–Meier method, and the symmetrical 95%CI was calculated according to the method of Greenwood. OS was defined as the time from the start of induction therapy to death or last follow-up, and DFS was defined as the time from remission after induction therapy to recurrence or death. Survival curves were compared using the log-rank test. Probability (P) values < 0.05 were considered statistically significant. Computations were performed using the BMDP PC-90 statistical program (BMDP Statistical Software, Los Angeles, CA).

RESULTS

Characteristics of Patients with AL

Information on 37 pregnant women with AL was collected in 13 French centers. The median patient age was 30 years (age range, 19–45 years). Pretreatment characteristics of the 37 patients are shown in Tables 1 and 2. The interval between the beginning of pregnancy and the diagnosis of AL ranged from 5 weeks to 37 weeks (median, 23 weeks). Nine patients had AL diagnosed during the first trimester, 10 patients had AL diagnosed during the second trimester, and 18 patients had AL diagnosed during the third trimester. There were no significant correlations between the age of pregnancy, features at registration, or types of treatment received after patients achieved CR (Table 3). The median interval between the diagnosis of AL and the onset of chemotherapy was 6 days.

Patient Outcomes and Prognostic Factors

Thirty-four patients (92%; 95%CI, 78–98%) achieved CR. Two patients had refractory disease, and there was one toxic death during induction. For postremission therapy, 23 patients received consolidation regimens with or without maintenance chemotherapy, and 11 patients underwent high-dose consolidation with stem cell transplantation (SCT), including 6 autologous SCTs and 5 allogeneic SCT. The median time between diagnosis and SCT was 4.5 months (range, 3.2–6.9 months). The median DFS was not reached. The 3-year DFS rate was 65%, and the 5-year DFS rate was 54% (Fig. 1). Ten of 34 patients (29%) who had achieved CR subsequently developed recurrent disease, including 6 patients who had received consolidation chemotherapy alone and 4 patients who had received high-dose consolidation. The median time to recurrence was 11.9 months (range, 2.3–40.0 months). The OS rate was 64% at 3 years and 46% at 5 years (Fig. 2). At a median follow-up of 3.4 years, 12 of 37 pregnant women had died of leukemia.

TABLE 1
Initial Characteristics and Outcomes in 37 Patients with Acute Leukemia Diagnosed During Pregnancy

Patient no.	Age (yrs)	Pregnancy no.	AL type[a]	Weeks of Induction pregnancy at diagnosis	Induction therapy for AL	Pregnancy outcome	Fetal outcome	Patient outcome
1	19	2	AML 2	26	RBZ + AraC	SVD	Term infant	CR
2	28	1	AML 3	7	ATRA + DNR + AraC	SA	—	CR
3	38	2	AML 0	15	IDA + AraC	TA	—	CR
4	33	1	AML 3	9	ATRA + DNR + AraC	TA	Fetal demise	CR
5	33	3	AML 5	6	IDA + AraC	TA	—	CR
6	38	1	AML 5	28	IDA + AraC	CS	Premature birth	CR
7	33	1	AML 2	28	DNR + AraC	CS	Term infant	CR
8	38	2	AML 3	5	ATRA + DNR + AraC	TA	—	CR
9	25	1	ALL T	27	DNR + VCR + CPM + Pred	SVD	Premature birth	Refractory
10	30	1	AML 4	23	DXM + AraC	CS	Premature birth	CR
11	38	2	AML 4	26	DNR + AraC	SVD	Term infant	CR
12	27	2	AML 5	16	DNR + AraC + Eto	TA	—	CR
13	34	2	ALL pre-B	9	DNR + VCR + CPM + Pred	TA	—	CR
14	27	2	AML 3	28	ATRA	SVD	Term infant	CR
15	45	2	AML 2	36	DNR + AraC	CS	Term infant	Refractory
16	33	4	ALL pre-B	26	DNR + VCR + Aspa + Pred	CS	Premature birth	CR
17	21	1	AML 2	20	RBZ	SVD	Term infant	CR
18	35	2	AML 4	30	DNR + AraC	SVD	Term infant	CR
19	31	2	AML 1	32	DNR + AraC	CS	Term twins	CR
20	24	1	AML 2	26	DNR + AraC	SVD	Term infant	CR
21	28	1	AML 4	9	DNR + AraC	TA	—	CR
22	30	2	AML 2	18	DNR + AraC	SVD	Term infant	CR
23	25	1	AML 4	26	DNR + AraC	CS	Premature birth	CR
24	30	2	AML 2	26	IDA + AraC	SVD	Term infant	CR
25	22	1	AML 4	13	DNR + AraC + MIT	SA	Fetal demise	CR
26	25	1	AML 5	27	DNR + AraC	SVD	Premature birth	Toxic death
27	26	1	AML 2	17	IDA + AraC	TA	—	CR
28	32	4	AML 2	16	DNR + AraC + MIT	TA	—	CR
29	23	1	AML 4	37	DNR + AraC	SVD	Term infant	CR
30	30	1	ALL Ph^+ 10		DNR + VCR + CPM + Pred	TA	—	CR
31	21	1	AML 5	19	DNR + AraC	TA	—	CR
32	36	7	AML 2	36	DNR + AraC + MIT	CS	Term infant	CR
33	29	2	AML 4	26	DNR + AraC	SVD	Term infant	CR
34	21	1	ALL pre-B	28	DNR + VCR + CPM + Aspa + Pred	CS	Premature birth	CR
35	25	1	ALL T	9	DNR + VCR + CPM + Pred	TA	—	CR
36	30	1	AML 4	10	DNR + AraC	TA	—	CR
37	33	4	AML 1	22	DNR + AraC	SVD	Term infant	CR

AL: acute leukemia; AML: acute myeloid leukemia; RBZ: rubidazone; AraC: cytarabine; SVD: spontaneous vaginal delivery; CR: complete remission; ATRA: all-*trans* retinoic acid; DNR: daunorubicin; SA: spontaneous abortion; IDA: idarubicin; TA: therapeutic abortion; CS: Cesarean section; ALL: acute lymphoblastic leukemia; VCR: vincristine; CPM: cyclophosphamide; Pred: prednisone; DXM: daunoxome; Eto: etoposide; Aspa: L-asparaginase; MIT: mitoxantrone; Ph^+: positive for the Philadelphia chromosome.

[a] FAB (French-American-British) classification subtype.

The white blood cell (WBC) count at the time of diagnosis was the only parameter that was correlated with DFS: A WBC count $\geq 10 \times 10^9$/L was associated with a poor outcome ($P = 0.01$). Factors that were correlated adversely with OS were a WBC count $\geq 10 \times 10^9$/L ($P = 0.01$), the presence of circulating blasts ($P = 0.04$), and bone marrow leukemic cells $> 50\%$ ($P = 0.04$) at diagnosis. The age of pregnancy at diagnosis, the number of prior pregnancies, and the termination of pregnancy did not influence patient outcomes.

Termination of Pregnancy and Fetal Outcome According to the Trimester of Pregnancy during which AL was Diagnosed

AL diagnosed during the first trimester

Nine patients (median age, 31 years) were diagnosed during the first trimester (6 patients with AML and 3 patients with ALL) (Table 3). Six women had severe extrahematologic complications (World Health Organization [WHO] Grade $\geq \geq 3$) after the induction remission course: These complications included in-

TABLE 2
Cytogenetics of 37 Patients with Acute Leukemia

Diagnosis/subtype	Proportion (%)	Karyotype	No. of patients
AML			
Favorable-risk cytogenetics	36	t(15;17)	4
		t(8;21)	4
		inv(16)	3
Intermediate-risk cytogenetics	48	Normal karyotype	12
		Trisomy 8	1
		t(9;11)	1
		Monosomy 18	1
Unfavorable-risk cytogenetics	6	Complex karyotype	2
Unknown	10	Failure	3
ALL			
B-cell lineage ALL	67	Normal karyotype	2
		t(9;22)	1
		+ X	1
T-cell lineage ALL	33	t(10;11)	1
		Failure	1

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia.

fections (3 patients), hemorrhages (2 patients), and pericarditis (1 patients). The median time for leukocyte recovery ($\geq 1 \times 10^9$/L), granulocyte recovery ($\geq 0.5 \times 10^9$/L), and platelet recovery ($\geq 100 \times 10^9$/L) was 23 days. All patients achieved a CR. The median DFS was not reached, whereas the median OS was 53 months. Eight pregnancies were terminated actively, and there was one spontaneous abortion.

AL diagnosed during the second trimester

Ten patients with AML (median age, 28 years) were diagnosed during the second trimester (Table 3). Two women developed severe infections after the induction remission course. The median time for leukocyte recovery ($\geq 1 \times 10^9$/L) and for granulocyte recovery ($\geq 0.5 \times 10^9$/L) recovery was 32 days. The median time for platelet recovery ($\geq 100 \times 10^9$/L) was 27 days. All patients achieved CR. The median DFS was 40 months, and the median OS was 26 months. Five pregnancies were terminated actively, and there was one spontaneous abortion. There were three full-term, normal deliveries of normal newborns. One woman underwent a Cesarean section with delivery of a premature baby. Overall, all four healthy babies survived. All of the babies had been exposed to chemotherapeutic agents.

AL diagnosed during the third trimester

Eighteen patients (median age, 30 years) were diagnosed during the third trimester (15 patients with AML and 3 patients with ALL) (Table 3). Seven women began chemotherapy after delivery: Three women (including 1 woman with a gemellary pregnancy) who were diagnosed at 30 weeks, 32 weeks and 37 weeks did not require immediate treatment and had full-term pregnancies with normal delivery; 2 women were diagnosed at term after normal delivery of morphologically normal babies; and 2 women underwent Cesarean section with delivery of a premature baby. Eleven women began chemotherapy during their pregnancy, including 3 women who had had full-term pregnancies with normal delivery of morphologically normal babies, 2 women who had normal delivery of a premature infant, and 6 women who underwent a Cesarean section with delivery of full-term, normal

TABLE 3
Characteristics and Outcome of Pregnant Women with Acute Leukemia According to the Trimester of Pregnancy at Diagnosis

	Trimester in which AL was diagnosed		
Characteristic	First trimester	Second trimester	Third trimester
Type of leukemia			
AML	6	10	15
ALL	3	0	3
Previous pregnancy			
Yes	4	5	10
No	5	5	8
Prior history of MDS			
Yes	1	0	1
No	8	10	18
Cytogenetics[a]			
Favorable	2	4	4
Intermediate	2	3	7
Unfavorable	2	1	3
FAB classification[a]			
M1	1	1	1
M2	0	4	6
M3	3	0	1
/M4	2	2	5
M5	1	2	2
Termination of pregnancy			
TA or SA	9	6	0
CS or SVD	0	4	18
Response to induction			
CR	9	10	15
Refractory	0	0	2
Death	0	0	1
Postremission therapy			
Chemotherapy	6	8	9
Autologous transplantation	2	0	4
Allogeneic transplantation	1	2	2
Recurrence			
Yes	3	4	3
No	6	6	12

AL: acute leukemia; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MDS: myelodysplastic syndrome; FAB: French–American–British; TA: therapeutic abortion; SA: spontaneous abortion; CS: Cesarean section; SVD: spontaneous vaginal delivery; CR: complete remission.
[a] Determined in patients with AML.

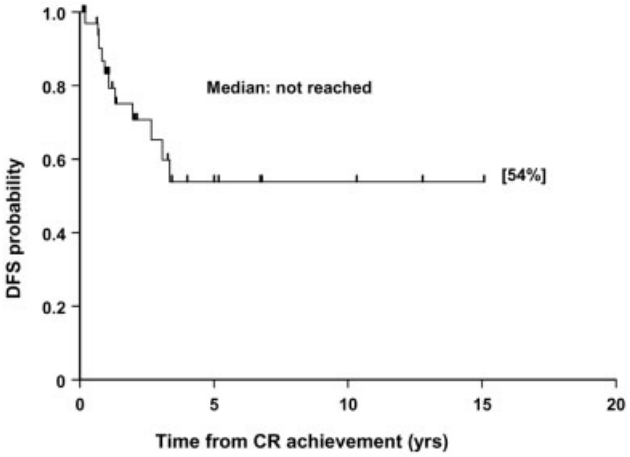

FIGURE 1. Kaplan–Meier estimate of disease-free survival (DFS) in the 34 complete responders. CR: complete response.

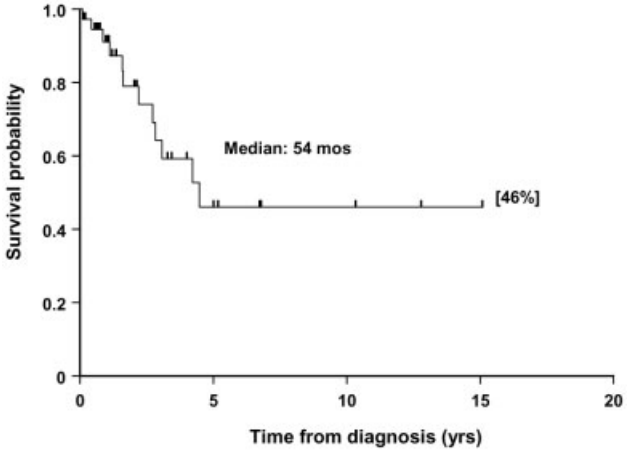

FIGURE 2. Kaplan–Meier estimate of overall survival (OS) in the 37 patients.

babies. Three women had severe extrahematologic complications (WHO Grade $\geq$ 3) after the induction remission course, including infection (1 woman), pulmonary fibrosis (1 woman), and portal thrombosis (1 woman). The median time for leukocyte recovery ($\geq 1 \times 10^9$/L) and for granulocyte recovery ($\geq 0.5 \times 10^9$/L) recovery was 25 days. The median time for platelet recovery ($\geq 100 \times 10^9$/L) was 22 days. Fifteen patients achieved CR, 2 patients had resistant disease, and 1 patient died from treatment toxicity 1 week after the normal delivery of a premature baby. The median DFS and the median OS were not reached. None of the babies (including the stillborns) presented with morphologic abnormalities, and the evolution has been normal with regard to growth and development in those who have been followed. Overall, 19 healthy babies survived, 11 of whom had been exposed to chemotherapeutic agents.

DISCUSSION

Since the first publication by Virchow in 1845, a rising number of patients with AL occurring during pregnancy have been reported. Data related to the main studies reported in the literature are presented in Table 4. AML accounts for more than two-thirds of leukemias that are seen during pregnancy,[10,11] and the diagnosis generally is made during the second and third trimesters.[10] This was confirmed in our study, in which 84% of patients had AML and 16% of patients had ALL, with 76% of patients diagnosed during the second or third trimesters. The proportions of favorable and normal karyotypes were 38% and 43%, respectively, and were similar to those generally observed.[9] Our results in terms of the CR rate (92%) and the long-term DFS rate (54%) were similar to previously reported results in patients with AL who were diagnosed during pregnancy[2,3,11–14] and were in accordance with general observations in patients in the same age bracket who were diagnosed with AL.

Delays or modifications in therapy to ensure the birth of a healthy infant may affect the maternal prognosis adversely.[15] Whereas some authors believe that pregnancy may accelerate the course of leukemia,[16] most authors do not find any support for this hypothesis.[2–4,6,10] Furthermore, patients have been reported in whom AL was transplanted from mother to child, presumably through the placenta.[17–19] In another patient, spontaneous remission of AL occurred after termination of pregnancy.[20] However, in that patient, the leukemia recurred rapidly, and the patient subsequently died.

Leukemia in a pregnant patient is supposed to increase the risk of abortion, fetal wastage, and perinatal mortality.[10,11,21] Fetal growth restriction and spontaneous preterm delivery reportedly occur in $\approx$ 40–50% of patients. In our series, only 2 spontaneous abortions were observed, but 13 terminations by medical decision were performed that involved all patients who were diagnosed during the first trimester and $\approx$ 50% of patients who were diagnosed during the second trimester.

The effects of cytostatic drugs on the fetus may be studied from two perspectives: immediate effects, which are well known in terms of abortion and teratogenicity, and late effects, which are less well known with potential gonadal and other endocrine disorders, growth and developmental problems, and genetic and teratogenic disorders that affect future generations.[5,22–24] The most critical period for teratogenicity is between the Weeks 3 and 10 of gestation, because this period correlates with the stage of active organogenesis. The occurrence of teratogenicity when che-

TABLE 4
Literature Regarding Acute Leukemia Diagnosed in Pregnant Women

Reference	No. of patients	AL type	Patient outcomes	Pregnancy and fetal outcomes
Catanzarite and Ferguson, 1984[21]	47	AL	Treated: 40 patients (OS > 12 mos)	5 TA, 3 perinatal demises, 1 live-born infant, 31 LI
			Untreated: 7 patients (1 survivor)	1 TA, 2 perinatal demises, 4 LI
Aviles and Niz, 1988[34]	17	AL	No mortality	No CM or late side effects
Reynoso et al., 1987[11]	58	AL	No mortality	50 live infants (42% term, 56% PB, 1 CM)
Siddiqui et al., 1990[33]	5	MDS	1 CR	3 SVD (1 Down syndrome), 1 TA, 1 hysterectomy
Caliguri and Mayer, 1989[10]	40	AML	72% CR in AML	13 Fetuses in first trimester, 8 PB, 2 SA
	20	ALL	76% CR in ALL	
Zuazu et al., 1991[35]	8	AML	2 Deaths	2 SA, 1 TA, 1 CS (1 PB), 3 SVD (3 LI), 2 maternofetal deaths
	1	ALL		
Camera et al., 1996[36]	1	ALL (recurrent)	1 Resistant	1 CS
Hansen et al., 2001[14]	1	ALL	1 CR	1 SVD
Fadilah et al., 2001[32]	16	APL	100% CR	No CM
Greenlund et al., 2001[12]	13	AML	9 CR (69%)	29% Fetal loss, no CM
Su et al., 2000[37]	2	ALL	2 CR	1 TA, 1 CS
Ali et al., 2003[38]	6	AML	5 CR, 5 deaths during therapy	3 SA, 6 TA, 1 LI
	4	ALL		
Yucebilgin et al., 2003[39]	1	AML	1 CR	1 CS
Current study	31	AML	34 CR (92%)	13 SVD, 2 SA, 13 TA, 9 CS
	6	ALL		

AL: acute leukemia; OS: overall survival; TA: therapeutic abortion; LI: living infant; CM: congenital malformation; PB: premature birth; MDS: myelodysplastic syndrome; CR: complete remission; SVD: spontaneous vaginal delivery; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CS: cesarean section; APL: acute promyclocytic leukemia.

motherapy is administered during the first trimester reportedly is 10–20%.[5,24] However, a review in 1988 showed that 86% of fetuses that were exposed to alkylating agents, 81% of fetuses that were exposed to an antimetabolite, and 83% of fetuses that were exposed to vinca alkaloids and antitumor antibiotics during the first trimester were free of malformations.[6] Combination therapy engenders a greater risk than single-agent therapy. Cytarabine and anthracyclines (except idarubicin) have not been associated with the occurrence of teratogenicity. Thus, the risk of fetal injury induced by the administration of cytotoxic chemotherapy during the first trimester of pregnancy is real but actually occurs in a minority of patients.[6] However, it has been suggested that therapeutic abortion should be offered to all patients who develop AL during the first semester.[25]

Successful treatment of AL in pregnant mothers is possible with the fetus in utero. Cytotoxic agents appear to be safer increasingly as the pregnancy approaches its term. Chemotherapy after the second trimester is not associated with an increased rate of fetal malformations.[5,6,24,26] Fetal hematopoiesis was not affected adversely, and no malformations were observed when chemotherapy was administered during the third trimester.[27] However, transient myelosuppression and increased risk of prematurity or stillbirth have been demonstrated.[5,13,21,28] Among the 23 conceptions observed in our series, 7 infants (30%) were born prematurely. When cytotoxic chemotherapy is administered near delivery, it is important to realize that the infant may be born neutropenic and/or thrombocytopenic. In our series, none of the 15 live infants (even among those who were born prematurely) who were exposed to chemotherapy presented with congenital abnormalities, and the follow-up revealed no subsequent malignancies.

Some situations require special attention. The management of APL during pregnancy represents a significant problem, because it usually is associated with coagulopathy and the potential teratogenic effect of chemotherapy and ATRA. Prior to the ATRA era, APL treated with standard chemotherapy did not always result in a live birth.[29,30] The successful use of ATRA for the treatment of APL during pregnancy was described first in 1994.[31] In a recent review, all patients with APL during pregnancy who were treated with ATRA alone or in combination with chemotherapy had favorable outcomes.[32] No teratogenic effect was observed. ATRA can be given during the second or

third trimesters of pregnancy with reasonable safety to the mother and the fetus. In our series, among four women who presented with APL, all received ATRA therapy and achieved a CR. Three of those four women were diagnosed during the first trimester and terminated their pregnancy by medical decision or spontaneous abortion. One woman was diagnosed with APL at 28 weeks of gestation and had a full-term pregnancy with normal delivery.

Another special situation is represented by myelodysplastic syndrome diagnosed during pregnancy. Indeed, an association has been suggested between myelodysplasia and pregnancy, and a few instances of spontaneous remissions have been observed after the termination of pregnancy.[20] However, three of five patients from the larger published series rapidly progressed to AL.[33] Similarly, 1 of our 2 patients (Patient 36) with initial myelodysplastic syndrome rapidly progressed to overt AML, whereas the other patient (Patient 15) was diagnosed at the time of delivery and progressed later.

Overall, attention must be paid to the drugs used and the age of pregnancy. We believe that each patient should be examined individually, considering both the aggressiveness of leukemia and the stage of the pregnancy when the therapy is applied. Despite the inherent limitations derived from this type of study, the data herein support the hypothesis that pregnant women in the first trimester should be offered termination of pregnancy because of the potential fetal consequences of chemotherapy and the maternal complications of leukemia. Chemotherapy treatment during the second to third trimesters, with fetal surveillance and monitoring for adequate growth, may not require termination, because remission of AL and delivery of a normal infant seem likely. During the last trimester, a slight delay in treatment should be considered to allow for delivery before the initiation of chemotherapy.

REFERENCES

1. Lichtman MA, Liesveld JL. Acute myelogenous leukemia. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ, Seligsohn U, editors. Williams hematology, 6th ed. New York: McGraw-Hill, 2001:1047–1084.
2. Aviles A, Neri N. Hematological malignancies and pregnancy: a final report of 84 children who received chemotherapy in utero. *Clin Lymphoma.* 2001;2:173–177.
3. Pizzuto J, Aviles A, Noriega L, Niz J, Morales M, Romero F. Treatment of acute leukemia during pregnancy: presentation of nine cases. *Cancer Treat Rep.* 1980;64:679–683.
4. Peleg D, Ben-Ami M. Lymphoma and leukemia complicating pregnancy. *Obstet Gynecol Clin North Am.* 1998;25:365–381.
5. Feliu J, Suarez S, Ordonez A, Garcia-Paredes LM, Gonzales-Baron M, Montero JM. Acute leukemia and pregnancy. *Cancer.* 1988;61:580–584.
6. Doll DC, Ringenberg S, Yarbro JW. Management of cancer during pregnancy. *Arch Intern Med.* 1988;148:2058–2064.
7. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of acute leukaemias. French-American-British (FAB) Co-operative Group. *Br J Haematol.* 1976;33:451–458.
8. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. *J Clin Oncol.* 2003;21:4642–4649.
9. Grimwade D, Walker H, Oliver F, et al. The importance of diagnostic cytogenetics on outcome in AML: analysis of 1612 patients entered into the MRC AML 10 trial. *Blood.* 1998;92:2322–2333.
10. Caligiuri MA, Mayer RJ. Pregnancy and leukemia. *Semin Oncol.* 1989;16:388–396.
11. Reynoso EE, Shepherd FA, Messner HA, Farquharson HA, Garvey MB, Baker MA. Acute leukemia during pregnancy: the Toronto Study Group experience with long-term follow-up of children exposed in utero to chemotherapeutic agents. *J Clin Oncol.* 1987;5:1098–1106.
12. Greenlund LJ, Letendre L, Tefferi A. Acute leukemia during pregnancy: a single institutional experience with 17 cases. *Leuk Lymphoma.* 2001;41:571–577.
13. Kawamura S, Suzuki Y, Tamai Y, Itoh J, Fukushima K, Takami H. Pegnancy outcome among long-term survivors with acute leukemia. *Int J Hematol.* 1995;62:157–161.
14. Hansen WF, Fretz P, Hunter SK, Yankowitz J. Leukemia in pregnancy and fetal response to multiagent chemotherapy. *Obstet Gynecol.* 2001;97:809–812.
15. Iseminger KA, Lewis MA. Ethical challenges in treating mother and fetus when cancer complicates pregnancy. *Obstet Gynecol Clin North Am.* 1998;25:273–285.
16. Rodriguez Fuchs CA. Leucemia aguda y embarazo. *Sangre.* 1988;33:56–57.
17. Osada S, Horibe K, Oiwa K, et al. A case of infantile acute monocytic leukemia caused by vertical transmission of the mother's leukemic cells. *Cancer.* 1990;65:1146–1149.
18. Sheikh SS, Khalifa MA, Marley EF, Bagg A, Lage JM. Acute monocytic leukemia (FAB M5) involving the placenta associated with delivery of a healthy infant: case report and discussion. *Int J Gynecol Pathol.* 1996;15:363–366.
19. Dildy GA III, Moise KJ Jr., Carpenter RJ Jr., Klima T. Maternal malignancy metastatic to the product of conception: a review. *Obstet Gynecol Surv.* 1989;44:535–540.
20. Antunes de Mayolo JA, Ahn YS, Temple JD, Harrington WJ. Spontaneous remission of acute leukemia after the termination of pregnancy. *Cancer.* 1989;63:1621–1623.
21. Catanzarite VA, Ferguson JE II. Acute leukemia and pregnancy. A review and management of outcome, 1972–1982. *Obstet Gynecol Surv.* 1984;39:663–678.
22. Yealez MW, Buckley JD, Woods WG, Ruccione K, Robison LL. History of maternal fetal loss and increased risk of childhood acute leukemia at an early age. *Cancer.* 1995;75:1718–1727.
23. Schleuning M, Clemm C. Chomosomal aberrations in a newborn whose mother received cytotoxic treatment during pregnancy. *New Engl J Med.* 1987;317:1666–1667.
24. Buekers TE, Lallas TA. Chemotherapy in pregnancy. *Obstet Gynecol Clin North Am.* 1998;25:323–329.

25. Jacobs C, Donaldson SS, Rosenberg SA, Kaplan HS. Management of the pregnant patient with Hodgkin's disease. *Ann Intern Med.* 1981;95:669–675.
26. Schafer AI. Teratogenic effects of antileukemic chemotherapy. *Arch Intern Med.* 1981;141:514–515.
27. Morishita S, Imai A, Kawabaa I, Tamaya T. Acute myelogenous leukemia in pregnancy: fetal blood sampling and early effects of chemotherapy. *Int J Gynecol Obstet.* 1994;44:273–277.
28. Lishner M, Koren G. Cancer chemotherapy during pregnancy. Consortium of cancer in pregnancy evidence. *Can Fam Physician.* 2001;47:41–42.
29. Hoffman MA, Wiernik PH, Kleiner GJ. Acute promyelocytic leukemia and pregnancy. A case report. *Cancer.* 1995;76: 2237–2241.
30. Giagounidis AAN, Beckmann MW, Giagounidis AS, et al. Acute promyelocytic leukemia and pregnancy. *Eur J Haematol.* 2000;64:267–271.
31. Stenloft J, Lanng Nielsen J, Hvidman LE. All-*trans* retinoic acid in acute promyelocytic leukemia in late pregnancy. *Leukemia.* 1994;8:1585–1588.
32. Fadilah SAW, Hatta AZ, Keng CS, Jamil MA, Singh S. Successful treatment of acute myelocytic leukemia in pregnancy with all-*trans* retinoic acid. *Leukemia.* 2001;15:1665–1666.
33. Siddiqui T, Elfenbein GJ, Noyes WD, Moreb JS, Oblon D, Weiner RS. Myelodysplastic syndromes presenting in pregnancy. A report of five cases and the clinical outcome. *Cancer.* 1990;66:377–381.
34. Aviles A, Niz J. Long-term follow-up of children born to mothers with acute leukemia during pregnancy. *Med Pediatr Oncol.* 1988;16:3–6.
35. Zuazu J, Julia A, Sierra J, et al. Pregnancy outcome in hematologic malignancies. *Cancer.* 1991;67:703–709.
36. Camera A, Campanile M, Catalano D, Mattace Raso A, Rotoli B. Relapse of acute lymphoblastic leukemia during pregnancy. *Eur J Gynecol Oncol.* 1996;17:303–305.
37. Su WL, Liu JY, Kao WY. Management of pregnancy-associated acute leukemia. *Eur J Gynecol Oncol.* 2002;24:251–254.
38. Ali R, Ozkalemkas F, Ozcelik T, et al. Maternal and fetal outcomes in pregnancy complicated with acute leukemia: a single institutional experience with 10 pregnancies at 16 years. *Leuk Res.* 2003;27:381–385.
39. Yucebilgin MS, Cagirgan S, Donmez A, et al. Acute myeloblastic leukemia in pregnancy: a case report and review of the literature. *Eur J Gynecol Oncol.* 2003;25:126–128.