Eur J Cancer Clin Oncol, Vol. 19, No. 7, pp. 881–884, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00

Acute Leukemia in Pregnancy: Report of Five Cases Treated with a Combination which Included a Low Dose of Adriamycin

ABDALLAH S. AWIDI,* MUSLEH S. TARAWNEH,† KANDIL S. SHUBAIR,* ABDULLAH A. ISSA† and YAHIA F. DAJANI†§

*Departments of *Internal Medicine, *Pathology and ‡Gynecology, Jordan University Hospital, Amman, Jordan*

Abstract—*Five cases of acute leukemia which developed in the course of pregnancy are reported. All five cases received combination therapy which included adriamycin. Two cases were treated during the first half of pregnancy. One of them aborted* 2 weeks *after commencing therapy but had severe homeostatic failure. The second had a successful pregnancy and delivered a normal infant. Three cases were treated during the second half of pregnancy. All had normal pregnancies and delivered normal infants. The babies have been followed up for periods ranging from* 1 month *to* 3 yr *and have shown normal growth and development.*

INTRODUCTION

ACUTE leukemia in pregnancy is uncommon. Management of a pregnant leukemic is difficult because of potential fetotoxicity of cytotoxic drugs. Administration of cytotoxic drugs during the first trimester is thought to be associated with a high rate of spontaneous abortion and fetal malformation [1]. However, when they are used during the second and third trimesters they are thought to be safe and cause little effect on pregnancy and fetus [1–3]. Several reports have appeared describing the safety of cytosine arabinoside and thioguanine during the second and third trimesters [4–13]. Reports about the safety of daunorubicin and adriamycin in pregnancy have been scarce [5, 7, 9, 10]. These drugs are becoming very important tools for treatment in acute leukemias.

We report on five cases of acute leukemia during pregnancy. All five patients received a combination of cytotoxic drugs that included adriamycin. Of these five cases four had successful pregnancy and delivered normal infants.

CASE REPORTS

Case 1

A 32-yr-old female, gravida 6 and para 5, was admitted to Jordan University Hospital (JUH) on 14 December 1977 with a 3-week history of exertional dyspnea and dizziness. Physical examination revealed severe pallor and splenomegaly. Examination revealed a 16-week size uterus. The hemoglobin was 5.8 g/dl; WBC 45×10^9/l. Bone marrow aspirate revealed hypercellular marrow with 86% lymphoblasts. On 21 December 1977 induction therapy was started with adriamycin 50 mg slow i.v. injection on day 1, vincristine 2 mg i.v. weekly for a total of 4 doses, prednisolone 40 mg daily for 4 weeks, L-asparaginase 14,000 units on alternate days for a total of 7 doses and allopurinol 300 mg daily. Remission was achieved on 29 January 1978, when a second course of therapy was given as in the first one. The patient was maintained on cyclophosphamide 300 mg weekly, methotrexate 30 mg weekly and mercaptopurine 75 mg daily. On 20 May 1978 she delivered a normal female infant weighing 3200 g. On 26 September 1978 she relapsed. Remission could not be achieved and she died on 16 December 1978. The baby is 40 months old and has normal development and growth.

Case 2

A 17-yr-old female primigravida was admitted to JUH on 31 March 1979 with a 3-week history of intermittent fever, vomiting and general malaise. Physical examination revealed mild pyrexia (37.5°C), generalized lymphadenopathy and splenomegaly. Length of gestation was estimated

Accepted 2 November 1982.
§Present address: Consulting Medical Laboratories, P.O. Box 9897, Amman, Jordan.

at 34 weeks. The hemoglobin was 9.5 g/dl; WBC 14×10^9/l. Bone marrow aspirate revealed 70% lymphoblasts. On 3 April 1979 the patient was given adriamycin 75 mg slow i.v. injection once on day 1, vincristine 2 mg i.v. weekly and prednisolone 60 mg daily. Remission was achieved 3 weeks later. On 25 April 1979 a normal male infant was delivered weighing 3300 g. The patient was given a second course of chemotherapy and was maintained on mercaptopurine 75 mg daily. She relapsed 4 months later and died of septicemia. The baby has been followed for nearly 32 months and has normal growth and development.

Case 3

A 16-yr-old female primigravida was admitted to JUH on 13 May 1979 with a 1-week history of jaundice and pyrexia. Physical examination revealed a severely ill patient with jaundice, pyrexia of 39.5°C, hepatosplenomegaly and generalized lymphadenopathy. The length of gestation was estimated at 35 weeks. The hemoglobin was 6.2 g/dl; WBC 2×10^9/l; platelets 59×10^9/l. The total bilirubin was 23.6 mg/dl with a direct of 18.01 mg/dl. Blood culture revealed *Pseudomonas aeroginosa*. Bone marrow aspirate was hypercellular, with 90% lymphoblasts. On 14 May 1979 the patient was given adriamycin 40 mg slow i.v. injection once on day 1, vincristine 2 mg i.v. weekly and prednisolone 60 mg daily for 4 weeks. Intravenous antibiotics were started on admission. On 15 June 1979 the patient delivered a normal male infant weighing 2900 g. Remission was achieved on 29 June 1979. The patient was given a second course and was maintained on mercaptopurine 50 mg daily. On 20 June 1980 she had CNS relapse and died. The baby has been followed up for 29 months and has normal growth and development.

Case 4

A 16-yr-old female primigravida was admitted to JUH on 17 December 1979 with a 2-week history of purpuric rash and dizziness. She developed a high temperature 1 week prior to admission. Physical examination revealed diffuse potechial rash and pyrexia of 39°C. There was prominent hepatosplenomegaly. The length of gestation was estimated at 16 weeks. The hemoglobin was 6.3 g/dl; WBC 34×10^9/l with 80% myeloblasts; platelets 16×10^9/l. The bone marrow was heavily infiltrated with myeloblasts with prominent Auer rods. Blood culture revealed *Pseudomonas aeroginosa*. On 20 December 1979 she was started on adriamycin 65 mg slow i.v. injection once on day 1, vincristine 2 mg i.v. weekly, prednisolone 100 mg daily, cytosine arabinoside 160 mg i.v. infusion daily for four days and i.v. antibiotics commenced on admission. The patient remained hemorrhagic and febrile with no clinical improvement. On the 12th hospital day she had vaginal bleeding and she aborted. The patient died shortly thereafter.

Case 5

A 28-yr-old female, gravida 6, para 5, was admitted to JUH on 24 October 1981 with an 8-week history of general weakness, palpitations and exertional dyspnea. Physical examination revealed pallor, gum hypertrophy, and cervical and axillary lymphadenopathy. The length of gestation was estimated at 24 weeks. The hemoglobin was 14.2 g/dl; WBC 16×10^9/l. Bone marrow aspirate revealed erythroleukemia. On 28 October 1981 the patient was started on a single dose of adriamycin 50 mg i.v. infuse over 1 hr on day 1, cytosine arabinoside 100 mg i.v. 12-hourly for 5 days, thioguanine 80 mg 12-hourly for 5 days and allopurinol 300 mg daily. She was also given a blood transfusion. On November 10, the bone marrow was in remission. She received the second course of chemotherapy on 28 November 1981 and the third on 19 December 1981. On 13 January 1982 she delivered a normal female infant weighing 2980 g. The patient was maintained on monthly courses of cytosine arabinoside 100 mg i.v. daily for 5 days and thioguanine 120 mg orally daily for 5 days. The patient is still in remission.

DISCUSSION

The optimal therapy for pregnant leukemic patients remains uncertain. Lilleyman *et al.* [8] reviewed 32 patients with acute myelogenous leukemia presenting during the first half of pregnancy. They found that the chance of producing a healthy baby is slightly less than 50%. When cytotoxic drugs were used during the first trimester they were associated with a high rate of spontaneous abortion and fetal malformation. Therapeutic abortion is usually advised.

Most of the data accumulated to date concerns the use of mercaptopurine, cytosine arabinoside and thioguanine during the second and third trimesters. They appear to be safe [1–4, 6–8, 11–13]. Manoharan and Leyden [14] reviewed 25 cases of acute non-lymphocytic leukemia reported in the literature and one of their own cases. These were managed during the second and third trimester. Of those treated with intensive chemotherapy 6 out of 7 cases had successful pregnancy with a normal infant.

Experience with anthracylines in pregnancy is limited. Only 5 cases have been described in the literature in which anthracyclines were used

[5, 7, 9, 10]. Four out of five cases delivered normal infants.

Table 1 shows the clinical details and therapy of our patients. Table 2 shows the cases described in the literature. It is of interest that all our cases received adriamycin as part of the cytotoxic regime. Two of our cases (cases 1 and 4) were treated during the first half of pregnancy. Case 1 had a successful pregnancy and delivered a normal child who, at follow-up, is perfectly normal. In case 4 abortion was thought to be secondary to hemostatic failure rather than primary drug toxicity. Cases 2, 3 and 5 were treated during the second half of pregnancy and all had normal infants. The child of case 3 has been followed up for more than 2½ yr, case 2 for nearly 3 yr and case 5 for about 1 month. They are all normal. Out of the 4 patients who delivered normal babies 3 died after a short remission (7, 4 and 12 months in cases 1, 2 and 3 respectively). The short survival of these patients constitutes a serious problem regarding the welfare and upbringing of their children. Every effort should be made to prolong remission by using more intensive chemotherapy after delivery.

Since anthracyclines form an important part in the therapy of acute leukemia the clarification of their safety in pregnancy is most important. It seems from our cases and others described that these drugs are probably safe in pregnancy.

In conclusion, we suggest that intensive cytotoxic drugs therapy that includes adriamycin is not incompatible with normal pregnancy and the delivery of normal infants.

Table 1. *Five cases of acute leukemia managed during pregnancy at JUH*

Case No.	Diagnosis	Length of gestation (weeks)	Treatment	Remission status at term	Outcome of pregnancy
1	ALL	16	ADR, VCR, Pred., L-Anase	complete remission	normal female infant, weight 3200 g
2	ALL	34	ADR, VCR, Pred.	complete remission	normal male infant, weight 2900 g
3	ALL	35	ADR, VCR, Pred.	partial remission	normal male, 3300 g
4	AML	16	ADR, VCR, Pred., Ara-C	died	abortion at 17th week
5	erythroleukemia	26	Ara-C, TG, ADR	complete remission	normal female, weight 2900 g

ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; Ara-C = cytosine arabinoside; ADR = adriamycin; VCR = vincristine; Pred. = prednisolone; TG = thioguanine; L-Anase = L-asparaginase.

Table 2. *Cases of acute leukemia in pregnancy treated with a combination which included anthracyclines*

Reference	Diagnosis	Length of gestation (weeks)	Treatment	Remission status	Outcome of pregnancy
[7]	AML	23	Ara-C, DNR, TG	complete	normal infant, 2967 g
[5]	ALL	21	ADR, VCR, Pred.	complete	normal, 2400 g but had high bilirubin
[9]	ALL not specified	12	Ara-C, ADR, VCR, Pred.	complete	normal, 2860 g
[10]	AML	27	DNR, Ara-C, TG	complete	normal but overweight, 5000 g
	ALL	15	DNR, Ara-C, TG	complete	died at 30th week

Ara-C = cytosine arabinoside; DNR = daunorubicin; ADR = adriamycin; VCR = vincristine; Pred. = prednisolone; TG = thioguanine.

Table 3. Summary of induction and maintenance therapy of 5 cases of acute leukemia during pregnancies

Case No.	Induction	Maintenance
1	1st course: ADR 50 mg slow i.v. infection on day 1, VCR 2 mg i.v. weekly for 4 weeks, Pred. 40 mg orally daily for 4 weeks, L-Anase 14,000 units alternate days total of 7 doses 2nd course: as in the first course	cyclophoshamide 300 mg orally weekly, Mtx 300 mg orally weekly, Mp 75 mg orally daily
2	1st course: ADR 75 mg slow i.v. injection on day 1, VCR 2 mg i.v. weekly for 3 weeks, Pred. 60 mg orally daily for 3 weeks 2nd course: as in the first course	MP 75 mg daily (post-delivery)
3	1st course: ADR 40 mg slow i.v. injection on day 1, VCR 2 mg i.v. weekly for 4 weeks, Pred. 60 mg orally daily for 4 weeks 2nd course: (post-delivery) as in the first course	MP 50 mg daily (post-delivery)
4	1st course: ADR 65 mg slow i.v. injection on day 1, VCR 2 mg i.v. weekly, Pred. 100 mg orally daily, Ara-C 160 mg i.v. infusion daily for 4 days	patient died. No maintenance
5	1st course: ADR 50 mg i.v. infusion over 1 hr on day 1, Ara-C 100 mg i.v. 12-hourly for 5 days, TG 80 mg orally 12-hourly for 5 days 2nd and 3rd courses: as in the first course	monthly Ara-C 100 mg i.v. for 5 days, TG 120 mg orally daily for 5 days

ADR = adriamycin; VCr = vincristine; Pred. = prednisolone; L-Anase = L-asparaginase; TG = thioguanine; MP = mercaptopurine; Ara-C = cytosine arabinoside; Mtx = methotrexate.

REFERENCES

1. NICHOLSON JD. Cytotoxic drug in pregnancy. *J Obstet Gynecol Br Cwlth* 1966, **75**, 307–312.
2. BITRAN JD, ROTH DG. Acute leukemia during reproductive life: its course, complications and sequelae for fertility. *J Reprod Med* 1976, **17**, 225–231.
3. MCLAIN C JR. Leukemia in pregnancy. *Clin Obstet Gynecol* 1974, **17**, 185–194.
4. AU-YONG R, COLLINS P, YOUNG JA. Acute myeloblastic leukemia during pregnancy. *Br Med J* 1972, **4**, 493–494.
5. DARA P, SLATER LM, ARMENTROUT SA. Successful pregnancy during chemotherapy for acute leukemia. *Cancer* 1981, **47**, 845–846.
6. DURIE BG, GILES HR. Successful treatment of acute leukemia during pregnancy. *Arch Intern Med* 1977, **17**, 90–91.
7. GOKAL R, DURRANT J, BAUM JD, BENNETT MJ. Successful pregnancy in acute monocytic leukemia. *Br J Cancer* 1976, **34**, 299–302.
8. LILLEYMAN JS, HILL AS, ANDERTON JK. Consequences of acute myelogenous leukemia in early pregnancy. *Cancer* 1977, **40**, 1300–1303.
9. NEWCOMB M, BALDUCCI L, THIGPEN T, MORRISON FS. Acute leukemia in pregnancy: successful delivery after cytarabine and doxorubicin. *JAMA* 1978, **239**, 2691–2692.
10. O'DONNELL R, COSTIGAN C, O'CONNELL LG. Two cases of acute leukemia in pregnancy. *Acta Hematol* 1979, **61**, 298–300.
11. PAWLINGER DF, MCLEAN FW, NOYES WD. Normal fetus after cytosine arabinoside therapy. *Ann Intern Med* 1977, **74**, 1012.
12. RAICH PC, CURET LB. Treatment of acute leukemia during pregnancy. *Cancer* 1975, **36**, 861–862.
13. TAYLOR G, BLOM J. Acute leukemia during pregnancy. *South Med J* 1980, **73**, 1314–1315.
14. MANOHARAN A, LEYDEN MJ. Acute non-lymphocytic leukemia in the third trimester of pregnancy. *Aust NZ J Med* 1979, **9**, 71–74.