

Safety of cytotoxic chemotherapy during pregnancy

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Abstract

Objective: To present an experience and results of treatment of pregnant cancer patients with cytotoxic chemotherapy from second trimester of pregnancy.

Methods: Eighteen consecutive pregnant patients treated at Khyber Teaching Hospital, Peshawar between December 2000 and August 2006 for different types of malignancies are reported. Six patients (33%) had breast cancer, four (22%) had chronic myeloid leukaemia, two (11%) had Hodgkin's disease, two (11%) had acute myeloid leukaemia and one each had recurrent ovarian carcinoma (5.7%), soft-tissue sarcoma (5.7%), acute lymphoblastic leukaemia (5.7%) and non-Hodgkin's lymphoma (5.7%). Various chemotherapeutic protocols were administered from second trimester of pregnancy onwards. Detailed obstetrical examinations and high risk foetal ultrasound monitoring were performed regularly.

Results: Two patients were lost to follow-up after one course of chemotherapy while two patients chose to have therapeutic abortion. Out of the remaining 14 patients, one patient had spontaneous abortion while one patient had an intra-uterine death of foetus during chemotherapy. Remaining 12/14 (86%) patients gave birth to live, healthy babies and no foetal malformations were observed. Six out of 140 breast cancer patients (4.3%) during the study period had concomitant pregnancy. Four patients with breast cancer had modified radical mastectomy with axillary dissection during pregnancy (median gestational age 22 weeks) and no operative or post-operative complications were noted. Three out of four breast cancer patients (75%) had hormone receptor negative tumours.

Conclusion: Chemotherapy during the second and third trimester of pregnancy can be safe if proper obstetric and radiologic monitoring is performed. Long term side-effects in these children need to be studied with extended periods of follow-up (JPMA 57:449:2007).

Introduction

During the reproductive age, cancer is the second commonest cause of death in women and complicates approximately 0.1% of all pregnancies.^{1,2} The occurrence of cancer during pregnancy presents a dilemma both to the treating physician and the patient. Delay or modification in treatment protocol in order to assure the birth of a healthy baby might result in poor prognosis for the mother. On the other hand, administration of cytotoxic chemotherapy might result in serious, even fatal, foetal complications.

Several studies have now shown conclusively that majority of cytotoxic drugs can be safely administered to pregnant patients in need of chemotherapy, specially breast cancer and haematological malignancies, from the second trimester onwards.³⁻⁵ Maternal or foetal complications have been reported to be very few in these studies. This is because organogenesis is completed by 10th -12th week of gestation and chemotherapy after this time usually does not cause any major organ damage in the foetus. This article presents a single center experience of 18 pregnant patients with various types of malignancies treated with different cytotoxic regimes from the second trimester of pregnancy onwards.

Patients and Methods

Eighteen consecutive pregnant patients were treated with various cytotoxic agents between December 2000 and August 2006 for different types of malignancies at Khyber Teaching Hospital, Peshawar. All female patients of age 18 years or more, with foetal gestational age of 12 weeks and above, with normal routine blood and biochemical profile and who had a biopsy or bone marrow proven malignancy were included. All patients had a tissue biopsy or bone marrow aspiration performed, as required. Every patient had a complete physical examination and obstetrical consultation. Genetic counseling which included the effects of chemotherapeutic agents on pregnancy and the foetus (including intrauterine death or foetal abnormalities), was provided. Patients were given the option of terminating the pregnancy if they desired. Chemotherapy was administered as required if the patient wished to continue with pregnancy after full explanation of the pros and cons of either terminating pregnancy or continuing with the pregnancy and chemotherapy. Routine investigations including complete blood count, renal and liver function tests and abdominal ultrasound were performed. Breast masses were

assessed by ultrasonography. Assessment of gestational age was done by ultrasonography. X-rays were avoided wherever possible. High risk obstetrical care with foetal surveillance was provided to each patient. Serial foetal growth ultrasounds were performed every three weeks to ensure the normal development and well-being of the foetus.

Various chemotherapeutic protocols were administered from second trimester of pregnancy onwards (until 37th week of gestation) as per protocol for the type of malignancy. Chemotherapy was withheld from the 37th week of pregnancy till 3-4 weeks after delivery in order to avoid chemotherapy related neutropenia or thrombocytopenia during delivery. Chemotherapeutic drugs used included: all-trans retinoic acid (ATRA), Hydroxyurea, Doxorubicin, Daunorubicin, Bleomycin, Vincristine, Cyclophosphamide, 5-Fluorouracil, Dacarbazine (DTIC), Cytarabine and Etoposide. Dose and method of administration of each regimen was the same as for non-pregnant patients. Routine medications for prevention of nausea and vomiting (metoclopramide or tropisetron and dexamethasone) and for chemotherapy related side-effects were administered as required. Blood counts, renal and hepatic functions as well as foetal growth were monitored regularly.

Type and stage of malignancy, gestational age at presentation, gestational age at surgery, types of cytotoxic drugs administered, number of cycles administered to each patient, complications during pregnancy, gestational age at labour, delivery complications and outcome of the delivery including any clinical foetal malformations were noted.

Results

A total of eighteen patients presented with malignancy and concomitant pregnancy from December 2000 to August 2006. Six patients (33%) had breast cancer, four (22%) had chronic myeloid leukaemia (CML), two (11%) had Hodgkin's disease (HD), two (11%) had acute myeloid leukaemia (AML), and one each had recurrent ovarian carcinoma (5.7%), soft-tissue sarcoma (STS; 5.7%), acute lymphoblastic leukaemia (ALL; 5.7%) and non-Hodgkin's lymphoma (NHL; 5.7%). Four (22%) patients belonged to Afghanistan, 4 (22%) to Peshawar, 3 (17%) to Malakand/Dir, two each (11% each) to Khyber Agency, Mohmand Agency and Waziristan and one (6%) to Bannu. Demographic data of these patients is shown in the Table.

Three patients with breast cancer had stage IIIA disease while one each had stage IIB, IIIC and stage IV disease. All four CML patients were diagnosed in chronic phase. Both patients with HD had stage IIIB disease, one patient with NHL had stage IIIA disease while amongst two

Table. Demographic characteristics of patients treated with various chemotherapy protocols during pregnancy.

Characteristics	Range	Mean	+/-S.D
Age of patients	20 - 32 years	26	3.6
Gestational age at chemotherapy	12 - 33 weeks	23	5.9
Gestational age at surgery (MRM)	17-29 weeks	22	4.9
Gestational age at delivery	36 - 39 weeks	38	1.03

AML patients one had M2 and one had M3 sub-type. One patient each diagnosed with ALL had L2 sub-type, with STS had stage III and recurrent ca. ovary patient had stage IIC disease.

Out of a total of 140 patients presenting with breast cancer during the study period, 06 (4.3%) patients had concomitant pregnancy with breast cancer. Of the six breast cancer patients, two received FAC (5-Fluorouracil, Adriamycin, Cyclophosphamide) chemotherapy in neo-adjuvant setting (one patient had metastatic carcinoma while the second had locally advanced T4 inoperable lesion). Four patients had modified radical mastectomy (MRM) with axillary clearance, without any complications, followed by FAC chemotherapy in adjuvant setting. Mean gestational age at the time of MRM was 22 ± 4.9 weeks). No operative or post-operative complications were reported for any of these four patients. Four patients had hormone receptor status available. Three were ER/PR negative (75%) while one was ER positive and PR weak positive. Three patients had Her-2 neu status available and all three were negative for Her-2 receptor.

Breast cancer patients received a mean of 04 cycles of FAC chemotherapy (range 2-6). HD patients received a median of 7.5 cycle of ABVD (adriamycin, bleomycin, vinblastin, dacarbazine) chemotherapy (range 7-8). AML patients received one cycle of chemotherapy with cytarabine and daunorubicin. ALL patients received 04 cycles of vincristin, daunorubicin and prednisolone induction chemotherapy and one cycle of intensification. NHL patients received 03 cycles of CHOP (cyclophosphamide, oncovin/vincristin, doxorubicin, prednisolone) chemotherapy while STS patients received one cycle of CyVADIC (cyclophosphamide, vincristin, doxorubicin, dacarbazine) chemotherapy. All CML patients received oral Hydroxyurea while one AML (M-3) patient received oral all-trans retinoic acid (ATRA).

Chemotherapy cycles were given to all patients, irrespective of the type of malignancy, till 37th week of gestation after which chemotherapy was withheld till after the delivery. This was done in order to protect the patient and the foetus from chemotherapy induced neutropenia or thrombocytopenia which may have resulted in massive haemorrhage or serious infection at the time of delivery.

Out of eighteen patients, two patients (recurrent ca. ovary and AML) chose to have termination of pregnancy before administration of chemotherapy (weeks 12 and 32 respectively) while two patients (AML and NHL) were lost to follow-up (after one and three courses of chemotherapy respectively). Out of the remaining 14 patients, one patient (soft tissue sarcoma) had a spontaneous abortion two weeks after first cycle of chemotherapy (week 22) while one (ALL) had an intra-uterine death of foetus (week 35) during chemotherapy. Remaining 12/14 (86%) patients gave birth to live, healthy babies. Eleven patients had normal vaginal deliveries while one had a caesarian section due to foetal distress at week 38 but delivered a live normal baby. No foetal malformations were observed. No unusual complications were reported post-term. Five babies were male (42%) while seven (58%) were female. Since majority of deliveries (8/12) took place in home town of the patients, therefore no details regarding birth weight or Apgar score of the babies could be provided. Breast feeding was not allowed since the patients were on cytotoxic therapy. No adverse effects of pregnancy on the outcome of cancer treatment were noted in any of the patients treated while being pregnant.

Of the 12 live births, two babies died of infectious complications (unrelated to pregnancy) one at two months and second one at three months, while one baby died of accidental death. Four babies were lost to follow-up. Five babies are currently being followed-up all having normal growth pattern with no physical or neurological deficits. The eldest baby being followed up is 42 months old. Two patients (one each with HD and CML) became pregnant again. Both gave birth to live, normal, healthy babies.

Discussion

The incidence of cancer with concomitant pregnancy is low (0.1% of all pregnancies). Most of the publications are based on case reports or a small number of patients. Literature from the western countries have reported the incidence of breast cancer during pregnancy to be between 3-7% and the disease is reported to be aggressive with adverse prognostic factors such as advanced stage of disease, axillary node involvement and hormone receptor negative tumours.^{3,5,6} Studies conducted in Pakistan have reported the incidence to be 6%^{7,8}, with patients presenting with a higher stage of malignancy at diagnosis (stage III in 70% patients). A large number of pregnant patients had axillary node involvement (75%) and 71% patients were hormone receptor negative, all adverse prognostic factors^{7,8}, which also concur with this study findings. Despite the high incidence of adverse prognostic factors, these studies have also shown that there was no difference in the outcome of the disease with no significant difference in overall survival

of patients with breast cancer with or without concomitant pregnancy.^{3,6,8} However the follow-up is short (3-5 years) and long term follow-up is necessary to validate this claim.

A pivotal study at M.D. Anderson Cancer Center showed that the use of FAC (5- Fluorouracil, Adriamycin, Cyclophosphamide) chemotherapy in 2nd and 3rd trimester of pregnancy in breast cancer patients posed no risk to the mother or unborn foetus.³ Modified radical mastectomy (MRM) performed on 18 patients in this study also had no detrimental effect on the mother or foetus. Various other studies have confirmed these results both for surgery^{3,6,9} and chemotherapy^{6,10} during pregnancy. A French national survey on treatment of breast cancer during pregnancy showed that 95% of pregnancies resulted in live births with low morbidity in the new born.¹¹ Similar results (although mostly case reports) were also shown for other malignancies including lymphomas, cervical cancer^{12,13}, gastric cancer¹⁴, chronic myeloid leukaemia^{15,16} and acute leukaemias.^{17,18} Different types of cytotoxic drugs were used in these studies according to the protocol for the particular malignancy in the 2nd and 3rd trimester and no major complications were reported. In a series of 32 patients with various types of malignancies during pregnancy, 97% were live births although the rate of premature deliveries was high at 82%.¹⁹ Some reports of intra-uterine deaths, foetal malformations or spontaneous abortions have also been reported in literature, although the overall incidence of these complications was low.^{15,18,20}

Pregnancy has not been proved to influence the outcome of majority of cancers studied. Comparing pregnant and non-pregnant women at similar stages and on chemotherapy, the prognosis is similar.^{8,18,21-23} Stopping of chemotherapy during pregnancy can result in loss of response in leukaemia patients.¹⁵

Intensification protocols for haematological malignancies should be avoided during pregnancy. But if it is absolutely necessary, then a decision must be taken on individual case basis. This is because increasing the dose beyond the normal threshold dose in the protocol increases foetal toxicity manifolds. Unfavourable outcome of the foetus is usually seen in acute leukaemia patients given intensifications with very high doses of cytotoxic drugs.⁴ Radiotherapy, if required, can be safely given after delivery.

Long term effects on the new born have rarely been studied. In one long term study, no neurological or psychological abnormalities were reported in 84 children.²⁴ After a follow-up of up to 29 years, no increased incidence of cancer was detected in these children. In another study, 3/10 children born after exposure to in-utero chemotherapy had some neurologic deficit and there was a tendency towards a thinner ventricular wall although the overall

cardiologic outcome of these children did not differ significantly from controls.²⁵

The results of this study regarding the outcome of chemotherapy during pregnancy with various types of malignancies also show a live birth rate of 86% with no major foetal complications or malformations. This is consistent with the data already published. Majority of our patients delivered at home in remote areas (albeit despite advice not to do so) but even then no major complication during delivery was reported.

In conclusion, pregnancy does not adversely affect the outcome of cancer patients. Chemotherapy in the 2nd and 3rd trimesters of pregnancy with high risk obstetrical and foetal ultrasound monitoring can be safe both for the mother and foetus. This has to be done with a multidisciplinary team approach including an oncologist, gynaecologist, surgeon and radiologist. Long term effects on these children need to be observed in prospective studies.

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