Letter to the Editor

A Pregnant Lady With Aggressive Breast Cancer

Dear Editor,

Breast cancer is known to occur in up to 1 in 3000 pregnancies and a few cases could be expected each year in our population. We describe how we managed a case recently. Multidisciplinary co-management enabled conventional oncologic treatment delivery and a good outcome. To our knowledge, this is the first such report in Singapore.

A 38-year-old lady, 6 weeks pregnant, was diagnosed with left breast cancer. Clinically there was progression over 3 weeks from a 1.5-cm lump to nodular hardening of the entire upper outer quadrant, and a palpable ipsilateral axillary lymph node. Mammography and ultrasound showed multiple left breast nodules and axillary lymphadenopathy. Breast biopsies revealed high-grade invasive ductal carcinoma (IDC), positive for oestrogen and progesterone receptors. She underwent mastectomy and axillary clearance at 8 weeks' gestation. Histopathology showed multifocal (largest 3 cm) IDC (grade II), with 4 out of 13 axillary lymph nodes involved. Surgical margins were clear. Obstetric ultrasound scan at 13 weeks' gestation confirmed the dates and viability of a singleton fetus. At the medical oncology assessment, she was asymptomatic and clinical examination unremarkable. Ultrasound scan of the liver was normal, and she declined having a chest X-ray and radionuclide bone scan. She was deemed to have stage IIIA (T2N2M0) breast cancer and counselled on the benefits and risks of adjuvant chemotherapy, to which she agreed. Baseline 2-dimensional echocardiography was done, and Porta-Cath insertion was performed under local anaesthesia. She consented to a chest X-ray with abdominal shielding. There were no lung metastases seen. She received 6 cycles of 3-weekly CAF chemotherapy from the 18th week of pregnancy onwards: cyclophosphamide (500 mg/m^2), adriamycin (50 mg/m^2 infused continuously over 72 hours) and 5-fluorouracil (500 mg/m^2). Anti-emetic prophylaxis was intravenous diphenhydramine and oral prochlorperazine. She did not experience any major or severe toxicities. The nadir blood counts were: haemoglobin 9.4 g/dL, neutrophils 0.37 x 10^9/L and platelets 111 x 10^9/L. Routine urine cultures were taken at each mid-cycle review. Breast examination was done regularly. Two fetal anomaly ultrasound scans done during chemotherapy did not reveal any structural malformations. Serial ultrasound growth scans (done at 22, 33 and 35 weeks' gestation) did not show intra-uterine growth restriction or oligo-hydramnios. Her last cycle of chemotherapy was given at 34 weeks' gestation and she went into spontaneous labour at 37 weeks, delivering a baby girl via normal vaginal delivery. Repeat echocardiography just before delivery showed normal maternal cardiac function. Maternal and neonatal full blood counts checked immediately after delivery were normal. The birth weight was 2445 g and Apgar scores were 9 at both 1 minute and 5 minutes of life. The postnatal period was uneventful. The Porta-cath was removed 3 weeks post-delivery. Adjuvant radiotherapy began 5 weeks post-delivery, and tamoxifen was started after completion of radiation.

Much experience has been gained over the years in the management of breast cancer in pregnancy. Avoidance of delayed diagnosis is critical. As the physiologic mammary changes in pregnancy can hinder the accuracy of clinical examination and mammography, ultrasound is a useful adjunct and guides percutaneous biopsies. Except for computed tomography (CT), most other radiologic investigations normally done for diagnosis or staging can be performed in the gravid state: e.g., mammography and chest X-ray with abdominal shielding, liver ultrasound, and non-contrast magnetic resonance imaging (MRI) (especially after the first trimester). Breast cancers in pregnancy tend to present in a more advanced stage, yet pregnancy itself does not adversely affect the cancer prognosis when compared with non-gravid subjects matched for age and stage.[1] Hence, we believe in an aggressive approach to oncologic treatment. Reassurance can be given that the cancer can be treated as for non-pregnant women, with some modifications to protect the developing baby. Early-stage disease should be approached with curative intent, and treatment need not be unduly postponed because of the pregnancy. Termination of pregnancy has not been shown to improve prognosis.[1,2] Close obstetric monitoring is important, with accurate dating to facilitate treatment planning.

Surgery can be performed safely during any trimester.[3,4] Mastectomy with axillary lymph node dissection may obviate the need for breast radiation in early stage node negative disease. Axillary dissection is important because nodal metastases are common. Radiation should ideally be delayed until postpartum. This is not a problem since adjuvant chemotherapy is usually given first. For conditions where the primary beam is outside the abdomen, if radiation is deemed necessary in the third trimester and cannot be delayed, it may be delivered with a low but potential risk of carcinogenesis. When not in the entry or exit portal of the radiation beam, the dose to the fetus may arise from external or internal scatter. External scatter is relatively insignificant compared with the radiation produced in the primary beam with modern linear accelerators, while the

clinical impact of internal scatter from breast irradiation to the fetus on organ development in the third trimester is estimated to be nil or minimal. The potential adverse effects of fetal irradiation are mostly in the first and second trimester.[5] Incidental doses that may be received by the third-trimester fetus from breast cancer tangents (<10 to 25 cGy) should not cause growth disturbance and organ abnormalities.[5] The main concern arises from the risk of carcinogenesis, with the additional risk of childhood malignancy estimated conservatively at 0.06% with dose at 1 cGy exposure.[5]

Most women with gestational breast cancer will require a course of chemotherapy as standard care. The risks of spontaneous abortion, intrauterine death, and major malformations are concentrated in the period of organogenesis. When chemotherapy is given after the first trimester, most papers report a safe profile,[6-8] with the incidence of major congenital malformations not higher than the baseline. Intrauterine growth restriction, prematurity, and low birth weight are still associated risks.[7,8] However, confidence in administering chemotherapy to pregnant breast cancer patients after the first-trimester is boosted by an unprecedented prospective trial using standard CAF.[4] Twenty-four patients tolerated full doses of chemotherapy without major complications. The incidences of preterm labor and pre-eclampsia were not increased. The infants had good Apgar scores and no birth defects. There was no increase in low-birth weight infants and no developmental abnormalities were reported in the children (median age, 4.5 years).[4] Other retrospective series of anthracycline-based chemotherapy report similar findings.[6] Doxorubicin (adriamycin) is the preferred anthracycline in pregnancy.[8] In one report, fetal and postnatal echo-cardiograms were performed until the infant was up to age of 2 years and no abnormalities were seen.[9] We gave doxorubicin at standard dose-intensity, and as a continuous infusion to reduce the cardiotoxicity risk. There was no maternal or fetal toxicity. The patient's prior pregnancy delivered a baby with similar birth weight and gestational age. Chemotherapy dosing was weight-based, taking into account the modest maternal weight gains as the pregnancy progressed. Full doses were maintained for curative intent and absence of toxicity. Chemotherapy cycles were timed, keeping in mind the recovery of neutropaenia (and possible thrombocytopaenia) by the time of the expected delivery date. The mother was told not to breastfeed since many cytotoxic drugs can enter breast milk. While three-weekly CAF (with infusional doxorubicin) is shown to be a safe regimen to use in gestational breast cancer,[4] methotrexate should be avoided throughout pregnancy,[6] and data on the safety of taxanes are limited.[7,10] Tamoxifen is contraindicated during pregnancy.

With diligent application of the available data, the pregnant patient with breast cancer can be treated with almost the same approach as for non-pregnant patients. Each case presents the managing team with the daunting yet potentially rewarding challenge of saving 2 lives instead of 1.

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