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Weekly epirubicin in the treatment of gestational breast cancer (GBC)

Fedro A. Peccatori · Hatem A. Azim Jr · Giovanna Scarfone ·
Angiolo Gadducci · Cristina Bonazzi · Oreste Gentilini · Viviana Galimberti ·
Mattia Intra · Marzia Locatelli · Barbara Acaia · Piero Rossi ·
Saverio Cinieri · Liliana Calabrese · Aron Goldhirsch

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Abstract *Background* GBC is a rare disease and chemotherapy in this setting lacks a standardized approach. *Patients and Methods* Patients 16–30 weeks pregnant with locally advanced/metastatic disease or with high risk of recurrence after surgery were evaluated. *Results* Twenty patients received weekly epirubicin 35 mg/m². Median maternal age was 37 years (23–42). Median gestational age at chemotherapy was 19 weeks. Thirteen patients were treated after surgery while 7 had locally advanced tumours of which one had liver metastases. Mean total epirubicin

dose was 420 mg/m² with a median number of 12 administrations (4–16). No grade 3–4 toxicities were observed. No foetal adverse events were observed except 1 premature delivery at 28 weeks. Births were induced by caesarean section in 12 patients at a median gestational age of 35 weeks. No malformations were reported except 1 newborn with polycystic kidney. At a median age of 2 years, neurological, cardiological and immunological development was normal in all children as reported by their parents. In 7/20 patients with evaluable disease, five had an objective response. At a median follow-up of 38 months, 17 patients are alive; 14 are disease free. *Conclusions* Weekly epirubicin appears safe and effective with low foetal toxicity and could be considered in GBC.

Fedro A. Peccatori and Hatem A. Azim Jr contributed equally to the work.

F. A. Peccatori (✉) · H. A. Azim Jr · M. Locatelli · S. Cinieri ·
L. Calabrese · A. Goldhirsch
Department of Medicine, European Institute of Oncology,
Via Ripamonti 435, 20141 Milan, Italy
e-mail: fedro.peccatori@ieo.it

G. Scarfone · B. Acaia · P. Rossi
Division of Obstetrics and Gynaecology, IRCCS Policlinico,
Mangiagalli and Regina Elena, University of Milan, Milan, Italy

A. Gadducci
Division of Obstetrics and Gynaecology, Pisa University,
Pisa, Italy

C. Bonazzi
Division of Obstetrics and Gynaecology, Bicocca University,
Monza, Italy

O. Gentilini · V. Galimberti · M. Intra
Division of Senology, European Institute of Oncology,
Milan, Italy

S. Cinieri
Division of Medical Oncology, Perrino Hospital, Brindisi, Italy

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Introduction

Breast cancer is the most frequent malignant tumour and the leading cause for cancer-related mortality in fertile women [1]. Breast cancer incidence increases with age and due to the current trend to delay pregnancy later in life [2], the rare coincidence of breast cancer and pregnancy has become more frequent [3]. GBC constitutes around 3–4% of breast cancer with around 1:3,000 women diagnosed by breast cancer during their pregnancy course [4]. In Italy, it could be estimated that approximately 100–200 new cases of gestational breast cancer are diagnosed every year [5].

The relative rarity of this event precludes the conduct of large prospective trials and thus current knowledge is mainly based on retrospective case-control studies or reviews of case series [6, 7].

While surgery can be safely performed during pregnancy [8] and radiotherapy is usually postponed after delivery [9], systemic chemotherapy for women affected by gestational breast cancer remains a clinical challenge. Due to their mechanisms of action, all chemotherapeutic agents are potentially toxic to the foetus and thus maternal advantage must be always weighed against the possible embryo-foetal risk.

Gestational age has a profound impact on the foetal toxicity. During the first trimester the administration of chemotherapy is associated with a high risk of miscarriage and/or malformations reaching 20% [10, 11]. During the second and third trimester, such risk is reduced to as low as 1%, which is similar to that of untreated population [7].

Few regimens, mostly anthracycline-based, have been administered in pregnant breast cancer patients with little or no foetal toxicity [12]. However, some safety considerations remain open, particularly the risk of premature delivery and long-term cardiac follow up of the newborns. Such concerns encourage the application of a customized approach to deliver an effective treatment for the mother with the least toxicity to the pregnancy and the foetus. Epirubicin is a well described anthracycline in the treatment of breast cancer and characterized by lower cardiotoxicity compared to doxorubicin [13]. Its weekly application ensures a lower epirubicin peak blood concentration [14] with lower maternal myelotoxicity and possibly lower placental transfer of the drug. Moreover, weekly scheduling allows close monitoring of the pregnancy, which reassures both the mother and the physician. Thus, for the past 6 years we have applied weekly single agent epirubicin in the treatment of GBC at our institutions and here we report the results of this regimen.

Patients and methods

Pregnant women with pathologically diagnosed breast cancer who received at least one administration of single agent weekly epirubicin were retrospectively evaluated. Patients were treated at the European Institute of Oncology, IRCCS Policlinico Mangiagalli and Regina Elena, Pisa and Bicocca Universities in Italy. Shared institutional policies warranted chemotherapy for pregnant women with locally advanced or metastatic breast cancer or with high risk of recurrence after surgery. The four participating institutions agreed by mutual consent to treat pregnant patients only between the 16th and the 30th week of gestation in order to reduce foetal damage in the first trimester and to avoid unnecessary foetal exposure to chemotherapy during the third trimester when the foetus can be safely delivered. Other common criteria for chemotherapy administration

included stable pregnancy and an ECOG performance status 0 to 2. Adequate bone marrow, liver and renal functions were also required before chemotherapy. Echocardiogram was performed prior to starting chemotherapy and at the end of the treatment course.

A tailored informed consent was signed by all patients according to each single institution policy illustrating the possible advantages for the mothers but also uncertainties about foetal and pregnancy outcome. Patients were treated outside a clinical trial and data were collected retrospectively by a single investigator.

Results

From January 2002 through December 2007, 20 patients were identified. Patient characteristics are summarized in Table 1. Median maternal age was 37 years (23–42). Median gestational age at breast cancer diagnosis was 12 weeks (5–30), while median gestational age at chemotherapy administration was 19 weeks (16–30). Thirteen out of 20 patients were treated after surgery because of high risk of relapse according to the St. Gallen recommendations [15]. Five out of 13 patients had positive axillary nodes of which 3 had >5 positive nodes. Six out of 20 patients had locally advanced disease and 1 patient had a locally advanced tumour with synchronous liver metastases. Ten out of 20 patients had an endocrine responsive disease with 4/20 over-expressing HER-2/neu. Ki67 was elevated (>20%) in 13/20 patients.

All patients received single agent epirubicin, 35 mg/m² as a short intravenous infusion on a weekly outpatient basis. Serotonin-receptor antagonists were usually administered

Table 1 Patient characteristics

Characteristics	Number (%)
Number of patients	20 (100%)
Age	Median: 37 Range: 23–42
Gestational age	Median: 19 weeks Range: 16–30
Treatment setting	Adjuvant: 13 (65) Lymph node positive: 5 (38) Lymph node negative: 8 (62) Locally advanced and/or metastatic: 7 (35)
Hormone receptor positive	10 (50)
Her-2/neu over-expression	4 (20)
Ki-67 status	>20%:13 (65) <20%:2 (10) Not done: 5 (25)

before chemotherapy. Mean total epirubicin dose was 420 mg/m^2 with a median number of 12 (4–16) delivered courses during pregnancy. No grade 3–4 toxicities were observed and no changes were encountered on post-treatment echocardiograms. One patient had grade 2 anaemia with response to erythropoietin. Nausea and vomiting were mild. No stomatitis was reported.

Chemotherapy was administered under strict monitoring of foetal condition by ultrasound and no foetal adverse events were observed with the exception of 1 premature delivery at 28 weeks of gestation. No pre-eclampsia or maternal hypertension was reported. Foetal alopecia was not observed even when reported in mothers. Births were usually induced by caesarean section (12/20) at a median gestational age of 35 weeks (28–40). Two of 20 newborns required neonatal intensive care, but none had pulmonary, cerebral or infectious complications. No neonatal malformations were observed, except for 1 newborn with polycystic kidney disease. At a median age of 2 years (0–4), neurological and immunological development was normal in all 20 children as reported by their parents.

Following delivery, women treated in the adjuvant setting continued chemotherapy for a total of six cycles. Standard chemotherapy regimens were offered for the remaining number of cycles with either AC (doxorubicin and cyclophosphamide) or FEC (5-Fluorouracil, epirubicin and cyclophosphamide) regimens.

In 7/20 patients with assessable disease, 5 had an objective response according to RECIST criteria with a response rate of 71%. Two out of these 5 patients achieved a clinical complete response. After a median follow-up of 38 months, 17 patients are alive (85%), of whom 14 are disease free (70%).

Discussion

Breast cancer during pregnancy remains a very critical clinical situation, especially when tumour characteristics require immediate systemic treatment. However, administration of chemotherapy to such patients lacks a standardized approach. Previously reported regimens are all adapted from non-pregnancy settings.

Anthracyclines, particularly doxorubicin and epirubicin are the most effective and widely used agents in the treatment of breast cancer. Nevertheless, they have a cumulative cardiac toxicity as they release free radicals, which may lead to irreversible myocardial damage [16]. During pregnancy the maternal heart is subjected to major stress to accommodate for an intensified demand [17] and might therefore be more vulnerable to anthracycline-related toxicity. Several methods have been adopted to reduce cardiac toxicity of anthracycline-based regimens, e.g.

prolonged infusions, weekly dose fractionation, liposomal formulations [18].

Prolonged infusion doxorubicin in GBC has been studied by a group at MD Anderson, Houston [19]. In this large prospective series, Hahn et al. treated 57 women with doxorubicin given at a dose of 50 mg/m^2 as continuous infusion for 72 h together with cyclophosphamide 500 mg/m^2 on day 1 and 5-fluorouracil 500 mg/m^2 on days 1 & 4. The results of this study showed that this regimen was both safe and effective. No cardiac events were reported, for the mother and for the newborn. All babies were healthy except for 3 congenital anomalies (Down syndrome, club foot and congenital uretral reflux).

In our experience, we adopted a single agent weekly low dose schedule and used epirubicin instead of doxorubicin. Epirubicin has a shorter terminal half-life than doxorubicin because of glucuronidation by the liver [20] and in pregnant women, by the placenta [21]. Furthermore, epirubicin has a better therapeutic index and fewer systemic and cardiac toxic effects [13]. As mentioned earlier, its weekly application decreases its potential adverse events and facilitates the monitoring of the pregnancy. Our preliminary results [22] using this regimen showed good clinical activity without any alteration in the pregnancy course or foetal adverse events, a fact that is further confirmed in this report. No pre-eclampsia was encountered in our series with only one pre-term delivery at 28 weeks, which compares favourably to the MD Anderson series [19]. At a median follow-up of 2 years, all children are alive with no acute or delayed toxicities. None of them had a congenital anomaly with the exception of one who had a polycystic kidney, a rather common and minor malformation. Nevertheless, follow-up is planned to all children to exclude delayed adverse events, although the limited available evidence suggests that exposure to anthracyclines during gestation does not seem to inversely affect the long term outcome of these children [23–25].

Finally, the weekly schedule is convenient for strict and thorough follow-up of pregnancies during the course of chemotherapy, potentially enabling the early identification of any pregnancy-related adverse event and is effective for reassuring the patients.

At a median follow-up of more than 3 years, 70% of patients remain disease free, which compares favourably to results of other standard regimens in a similar population of non-pregnant patients. Albeit the lack of evidence to support its use from the non-pregnancy setting, we believe that there is a reasonable rationale behind the selection of this regimen, as earlier illustrated.

To our knowledge, this is the second largest report addressing the feasibility and safety of a specific regimen in GBC. Based on these results, weekly epirubicin could serve as a relevant treatment option in this setting.

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