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

Fedro A. Peccatori, Hatem A. Azim, Giovanna Scarfone, Angiolo Gadducci, Cristina Bonazzi, Oreste Gentilini, Viviana Galimberti, Mattia Intra, Marzia Locatelli, Barbara Acaia, et al.

Breast Cancer Res Treat (2009) 115:591–594
DOI 10.1007/s10549-008-0159-2

CLINICAL TRIAL

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

Received: 29 May 2008 / Accepted: 6 August 2008 / Published online: 20 August 2008

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/m^2. 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/m^2 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.

Keywords Breast cancer · Pregnancy · Epirubicin · Chemotherapy · Safety · Foetus

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

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 chemotherapeutical 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/m^2 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 cyclophsophamide) 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.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Berkowitz GS, Skovron ML, Lapinski RH, Berkowitz RL (1990) Delayed childbearing and the outcome of pregnancy. N Engl J Med 322:639–664
3. Haas JF (1989) Pregnancy is association with newly-diagnosed cancer: a population-based epidemiologic assessment. Int J Cancer 34:229–235. doi:10.1002/ijc.2910340214
4. Loibl S, von Minckwitz G, Gwtn K, Ellis P, Blohmer JU, Schlegelberger B et al (2006) Breast carcinoma during pregnancy. International recommendations from an expert meeting. Cancer 106:237–246. doi:10.1002/cncr.21610
5. Boldrini R, Di Cesare M, Tamburini C (eds) (2007) Rapporto CeDAP, 2004. Italian Ministry of Health website (www.ministerosalute.it)
6. Ring AE, Smith IE, Jones A, Shannon C, Galani E, Ellis PA (2005) Chemotherapy for breast cancer during pregnancy: an 18-year experience from five London teaching hospitals. J Clin Oncol 23:4192–4197. doi:10.1200/JCO.2005.03.038
7. Cardonick E, Iacobucci A (2004) Use of chemotherapy during human pregnancy. Lancet Oncol 5:283–291. doi:10.1016/S1470-2045(04)01466-4
8. Cohen-Kerem R, Railton C, Oren D, Lishner M, Koren G (2005) Pregnancy outcome following non-obstetric surgical intervention. Am J Surg 190:467–473. doi:10.1016/j.amjsurg.2005.03.033
9. Orecchia R, Lucignani G, Tosi G (2008) Prenatal irradiation and pregnancy: the effects of diagnostic imaging and radiation therapy. Recent Results Cancer Res 178:3–20. doi:10.1007/978-3-540-71274-9_2
10. Doll DC, Ringenberg QS, Yarbo JW (1989) Antineoplastic agents and pregnancy. Semin Oncol 16:337–346
11. Zemlickis D, Lishner M, Degendorfer P, Panzarella T, Sutcliffe SB, Koren G (1992) Fetal outcome after in utero exposure to cancer chemotherapy. Arch Intern Med 152:573–576. doi:10.1001/archinte.152.3.573
12. Barthelmes L, Davidson LA, Gaffney C, Gateley CA (2005) Pregnancy and breast cancer. BMJ 330:1375–1378. doi:10.1136/bmj.330.7504.1375
13. Bonadonna G, Gianni L, Santoro A, Bonfante V, Bidoli P, Casali P et al (1993) Drugs ten years later: epirubicin. Ann Oncol 4:359–369
14. Twelves CJ, O'Reilly SM, Coleman RE, Richards MA, Rubens RD (1989) Weekly epirubicin for breast cancer liver metastasis and abnormal liver biochemistry. Br J Cancer 60:938–941
15. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ (2007) Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 18:1133–1144. doi:10.1093/annonc/mdm271
16. Myers C (1988) Role of iron in anthracycline action. In: Hacker M, Lazo J, Tritton T (eds) Organ directed toxicities of anticancer drugs. Martinus Nijhoff, Boston, Mass, pp 17–30
17. Clapp C, Thebault S, Martinez de la Escalera G (2007) Hormones and pospartum cardiomyopathy. Trends Endocrinol Metab 18:329–330. doi:10.1016/j.tem.2007.08.004
18. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C et al (2004) Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. Circulation 109:3122–3131. doi:10.1161/01.CIR.0000133187.74800.B9
19. Hahn KM, Johnson PH, Gordon N, Kuerer H, Middleton L, Ramirez M et al (2006) Treatment of pregnant breast cancer patients and outcomes of children exposed to chemotherapy in utero. Cancer 107:1219–1226. doi:10.1002/cncr.22081
20. Camaggi CM, Strocchi E, Comparsi R, Testoni F, Angelelli B, Pannuti F (1986) Biliary excretion and pharmacokinetics of 4′epidoxorubicin (epirubicin) in advanced cancer patients. Cancer Chemother Pharmacol 18:47–50. doi:10.1007/BF00253063
21. Kushari J, Mukherjea M (1980) Studies on beta-glucuronidase of the developing human placenta. Gynecol Obstet Invest 11:119–127
22. Peccatori F, Martinelli G, Gentilini O, Goldhirsch A (2004) Chemotherapy during pregnancy: what is really safe? Lancet Oncol 5:398. doi:10.1016/S1470-2045(04)01506-2
23. Partridge AH, Garber JE (2000) Long-term outcomes of children exposed to antineoplastic agents in utero. Semin Oncol 27:712–726
24. Gwyn K (2005) Children exposed to chemotherapy in utero. J Natl Cancer Inst Monogr 34:69–71. doi:10.1093/jncimonographs/lgi009
25. Aviles A, Neri N, Nambo MJ (2006) Long-term evaluation of cardiac function in children who received anthracyclines during pregnancy. Ann Oncol 17:286–288. doi:10.1093/annonc/mdj053