

Trastuzumab in the Treatment of Pregnant Breast Cancer Patients – an Overview of the Literature

Trastuzumab in der Behandlung schwangerer Mammakarzinompatientinnen – ein Literaturüberblick



Authors

Sophia S. Goller, Udo R. Markert, Karolin Fröhlich

Affiliation

Universitätsklinikum Jena, Klinik für Geburtsmedizin, Placenta-Labor, Jena, Germany

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Correspondence

Prof. Dr. Udo R. Markert
Universitätsklinikum Jena, Klinik für Geburtsmedizin,
Placenta-Labor
Am Klinikum 1, 07747 Jena, Germany
markert@med.uni-jena.de
www.placenta-labor.de

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ABSTRACT

Breast cancer is one of the most common malignancies which appear during pregnancy. Since women are increasingly not giving birth until they are at a more advanced age, it can be assumed that the incidence of pregnancy-related breast cancers will continue to increase in the future. Because of pregnancy-induced changes and conservative diagnosis, these carcinomas are frequently not detected until they are at an

advanced stage and thus generally require systemic adjuvant therapy. The available data on optimal chemotherapeutic management are limited. Particularly for the use of the target agent trastuzumab which could crucially contribute to improving the prognosis in the therapy of HER2-overexpressing breast cancer in non-pregnant women, there is a lack of definitive information regarding the profile of action and safety in pregnancy as well as with regard to any long-term effects on the child. Thirty-eight pregnancies on trastuzumab for the treatment of breast cancer were able to be analysed in the literature currently available. Information can be gained from this and conclusions can be drawn which can individualise and decisively improve therapeutic options in the future for the pregnant breast cancer patient.

ZUSAMMENFASSUNG

Das Mammakarzinom gehört zu den am häufigsten in der Schwangerschaft auftretenden Malignomen. Da Frauen zunehmend erst in fortgeschrittenem Alter gebären, ist anzunehmen, dass die Inzidenz schwangerschaftsassoziierter Mammakarzinome zukünftig weiter steigen wird. Aufgrund schwangerschaftsbedingter Veränderungen und zurückhaltender Diagnostik kommt es häufig dazu, dass diese Karzinome erst in fortgeschrittenen Stadien detektiert werden und somit meist einer systemischen adjuvanten Therapie bedürfen. Verfügbare Daten bezüglich des optimalen chemotherapeutischen Managements sind limitiert. Insbesondere zur Anwendung des Target-Agents Trastuzumab, welches in der Therapie des HER2-überexprimierenden Mammakarzinoms der nichtschwangeren Frau einen entscheidenden Beitrag zur Verbesserung der Prognose leisten konnte, fehlen dezidierte Informationen bezüglich des Wirk- und Sicherheitsprofils in der Schwangerschaft sowie auch hinsichtlich etwaiger Langzeiteffekte auf das Kind. Innerhalb der derzeit verfügbaren Literatur konnten 38 Schwangerschaften unter Trastuzumab zur Therapie eines Mammakarzinoms analysiert werden. Es lassen sich hieraus Informationen gewinnen und Rückschlüsse ziehen, die zukünftig die Therapieoptionen der schwangeren Mammakarzinompatientin individualisieren und entscheidend verbessern können.

Introduction

By definition, pregnancy-associated breast cancer (PABC) occurs during pregnancy or within one year after childbirth [1]. Based on all breast cancer diagnoses, fewer than 1% in Europe occur during pregnancy [2]. Nonetheless, along with carcinoma of the cervix and diseases of the hematopoietic system, breast cancer is one of the most frequently occurring malignancies during this time [1, 3, 4]. Breast cancer represents approximately 25% of all malignant diseases which occur during pregnancy [5].

The incidence of PABC is indicated in industrialised nations with values between 1:1000 and 1:3000 pregnancies, and many authors state a figure of 1:10000 pregnancies [5–12]. A steady increase in the incidence has been able to be recorded in recent decades. The reasons for this development include the increased occurrence of malignant diseases overall as well as the fact that women in industrialized nations more and more frequently do not decide on pregnancy until a more advanced age and a positive correlation with the incidence of breast cancer should be noted in this regard [10, 13–15]. The mean age of the woman at diagnosis is 33 years; the mean gestational age is 21 weeks [16].

Characteristics of Pregnancy-Associated Breast Cancer

Genetics

Approximately 5% of all breast cancers can be attributed to an autosomal-dominant inherited genetic disease [17]. Mutations in the genes BRCA1 and BRCA2 (breast cancer 1 and 2) are of primary importance for the hereditary breast cancer variants. In comparison to sporadically occurring malignancies, these manifest at a significantly younger age [18]. Overall, women with pregnancy-associated breast cancer more frequently carry these genetic predispositions than non-pregnant women from comparative populations [19].

Pathology

Histopathologically, PABC does not significantly differ from breast cancer in the non-pregnant woman. Many different types of breast cancer occur with similar frequency in pregnant as well as non-pregnant women [19,20]. Accounting for 70–90% of all cases, invasive ductal breast cancer is the most common type, followed by invasive lobular carcinoma. By contrast, inflammatory breast cancer occurs rather rarely [21,22].

Potential for metastasis

Just as in the case of breast cancer in the non-pregnant woman, PABC also metastasises most frequently to the lung, liver and skeletal system [23]. However, for pregnant women, in comparison to non-pregnant women from comparative collectives, there is a likelihood 2.5 times as great of being diagnosed at an already metastatic stage [24].

Pregnancy-induced changes to the breast tissue as well as the conservative use of diagnostic measures in pregnancy may be causes for the frequent delay in diagnosis which subsequently de-

termines the often already advanced tumour stage of the pregnant women [4, 12, 25].

Diagnosis

PABC presents most frequently as painless nodules in the breast and is discovered by the patient herself [26]. Therefore it is important that any abnormal findings on palpation during pregnancy which persist more than two to four weeks be clarified by means of an additional clinical examination, imaging, and tissue biopsy [23]. The literature indicates average figures for delay of diagnosis in pregnant women between two and fifteen months [27].

Staging

Imaging methods for the staging of breast cancer during pregnancy are indicated if they have an impact on subsequent therapeutic strategies. If the risk of metastasis is estimated as being low, there is fundamentally also the option of not performing staging examinations until after delivery and thus avoiding exposure of the foetus to any unnecessary radiation risks [4, 22].

Prognosis

Just as in the case of breast cancer in non-pregnant women, the prognosis of pregnancy-associated breast cancer depends above all on the size of the tumour, the differentiation, and the involvement of axillary lymph nodes [28]. The question as to whether the pregnancy per se has an influence on patients' prognosis was the subject of controversial debate in the 1980s and 1990s. Nowadays, it is largely assumed that the pregnancy per se should not be considered to be an indicator of a poor prognosis [2, 28–30].

Trastuzumab in the Breast Cancer Therapy of Pregnant Patients

General

Drugs which attack certain sites of the cellular signalling cascade in a targeted manner on the molecular level are becoming more important in the treatment of malignant diseases in general. These so-called target agents thus also play an ever larger role in the treatment of breast cancer. The considerations here focus on HER2, the human epidermal growth factor receptor 2, which has a crucial impact on the regulation of cell growth as well as cell differentiation. It is overexpressed in about 20–30% of all breast cancers [31]. The monoclonal antibody trastuzumab, among others, is targeted against this; this antibody has already significantly improved the prognosis of HER2-positive tumours to date and led to a considerable survival advantage for affected patients with HER2-overexpressing tumours [32, 33].

Trastuzumab has been approved in Germany since August 2000 for the treatment of HER2-overexpressing metastatic breast cancer, and since May 2006, it has also been approved for (neo-)adjuvant treatment in HER2-overexpressing tumours following surgery and standard chemotherapy as well as radiation therapy, if applicable [32, 34].

The exact molecular mechanism of action of this human monoclonal antibody is not yet entirely understood [35–37].

Mechanisms of action on an extracellular as well as an intracellular level are discussed. According to current data, the antineoplastic mode of action of the antibody, on the extracellular level, is based in particular on cell-mediated cytotoxicity [38,39]. By contrast, the intracellular mechanisms of action of trastuzumab are controversially described [31].

Another monoclonal antibody is pertuzumab, which is used together with trastuzumab and docetaxel in the first-line therapy of inoperable metastatic breast cancer [40]. It binds HER2 at another site than trastuzumab and as a result, it prevents the dimerisation of HER2 with other receptors of the HER family [41]. Various studies have already been able to prove the superiority of dual HER2 inhibition with trastuzumab and pertuzumab in non-pregnant women in comparison to the use of one of the two antibodies alone [42,43]. However, there are still no data on the use of pertuzumab in pregnancy.

In general, antibodies are used in pregnancy only very cautiously. This is due in particular to the currently limited data as well as to preclinical studies which are critical of the use of these active substances in pregnant women [44]. Thus a transplacental transfer of trastuzumab was also able to be demonstrated in earlier studies [9].

Indications

A precondition for HER2 antibody therapy is initially the quality-controlled determination of the HER2 status. Verification of the HER2 gene is necessary and this is done using fluorescence in situ hybridization (FISH) [34].

(Neo-)adjuvant therapy with trastuzumab is fundamentally indicated in patients with nodal-positive tumours and nodal-negative tumours ≥ 1 cm in diameter with HER2 overexpression. Treatment lasts one year and is generally carried out simultaneously or consecutively in combination with standard chemotherapy. Thus in this setting, the patients generally receive an anthracycline, followed by a taxane in combination with trastuzumab. Even if smaller tumours with a diameter of < 1 cm and HER2 overexpression are present, patients can benefit from therapy with trastuzumab following a benefit/risk assessment beforehand. Patients with HER2-overexpressing carcinomas which are already metastatic should also be treated with antibody therapy [34]. In these patients, a long, progression-free survival as well as overall survival were able to be demonstrated on trastuzumab [45]. As first-line therapy, in the metastatic stage, dual HER-2 blockade should take place in combination with a taxane.

Patient collectives

Breast cancer patients whose tumours demonstrate HER2 overexpression benefit from therapeutic strategies targeted against HER2 [32,33]. When selecting the patient collectives benefiting from this therapy, it should be borne in mind that the HER2 status may differ between the primary tumour as well as any metastases in up to 25% of cases, which is why metastases which subsequently occur should also be tested for possible HER2 positivity [46,47].

Courses of pregnancy on trastuzumab

► **Table 1** provides an overview of currently available data on the use of trastuzumab for the treatment of breast cancer during pregnancy. These data are based at this time primarily on case reports in which 22 pregnancies, including one twin pregnancy, are described [no. 1–18, 20–23]. Additional information was able to be obtained from the results of the international, multicentre, randomised phase III study called HERceptin Adjuvant (HERA). Among other things, it investigated the outcome of 16 children of patients who became pregnant during or up to three months after the administration of trastuzumab [no. 19]. In most cases, the antibody was administered to patients who were already in metastatic stages of the disease. Pregnant patients in early non-metastatic stages received trastuzumab more rarely. The case reports include 14 cases of exposure in the first trimester [no. 2, 3, 6–12, 14, 16, 18, 22, 23], whereby the vast majority of breast cancer patients on trastuzumab therapy became pregnant on an unplanned basis. In four patients, the treatment was discontinued after the pregnancy was discovered. Thirteen patients were treated only with trastuzumab, while in the remaining cases, double or triple combination regimens with vinorelbine, paclitaxel, docetaxel, tamoxifen, goserelin and carboplatin were used. One pregnant patient with cerebral metastases additionally received dexamethasone as well as cranial radiotherapy [no. 21]. Oligo- or anhydramnios were diagnosed in 13 of the total of 20 pregnancies [no. 2, 4, 5, 8–10, 12, 15, 17, 18, 20, 22, 23]; eight women were treated in the first trimester, seven received trastuzumab as monotherapy. In addition, there was also foetal intrauterine growth retardation (IUGR) in two cases; in one case in each instance, there was additional premature placental abruption, vaginal bleeding, premature rupture of membranes or foetal renal failure. Fifteen children were delivered via Caesarean section, on average in the 34th gestational week. Apart from one exception [no. 11], their birth weight was below 2700 g. In ten cases, there were neonatal complications; this included eight children of patients who developed oligo- or anhydramnios during pregnancy. All of these children suffered from respiratory complications [no. 4, 9, 10, 12, 13, 15, 16, 18, 23]. Three children concomitantly had renal failure [no. 4, 9, 12]. Four children died within the first four months of life [no. 9, 10, 12, 15]. The other children demonstrated normal development at follow-up examinations after an average of 22 months (2–84 months). One ectopic pregnancy was electively terminated. No pregnancy complications or anomalies were reported in the 16 patients of the HERA study [no. 19]. Nonetheless, a total of eleven abortions were recorded. Four of these were spontaneous abortions, seven were performed electively. However, the latter were not attributed to pregnancy complications, but instead to a particular degree of uncertainty and anxiety with regard to foetal trastuzumab exposure on the part of the patients as well as the attending physicians [48]. The five live births weighed an average of 3485 g and all demonstrated normal development. It should be noted overall that many complications which occurred could also be attributed to the preterm births of the children as such and cannot be attributed to the cytotoxic therapy alone.

► **Table 1** Trastuzumab for the treatment of PABC, overview of international case reports.

No.	Reference	n	Therapeutic regimen	Trimester of exposure	Receptors/metastasis	Pregnancy complications/anomalies	Delivery	Birth weight	Neonatal status/complications	Follow-up children
1	[75]	1	Trastuzumab + vinorelbin	3	ER-/PR-/HER2+, metastatic	None	Vaginal, W 34	2270 g (20th P)	None	6 mo: ND
2	[76]	1	Trastuzumab	Preconception, 1, 2	NI, metastatic	Anhydramnios (W 23)	Vaginal, W 37.5	2960 g (40th P)	None	6 mo: ND
3	[77]	1	Trastuzumab	Preconception, 1	NI, metastatic	None	Vaginal, NI	NI	None	NI
4	[78]	1	Trastuzumab + paclitaxel	2, 3	ER-/PR+/HER2+, metastatic	Anhydramnios, IUGR	Section, W 32	1460 g (10th P)	Bacteraemia, transient NRF, transient renal failure	3 mo: ND
5	[68]	1	Trastuzumab + docetaxel	2, 3	NI, metastatic	Anhydramnios (W 30), IUGR	Section, W 36	2230 g	None	NI
6	[79]	1	Trastuzumab	Preconception, 1, 2	ER-/PR-/HER2+, metastatic	None	Section, W 37	2600 g (10th P)	None	2 mo: ND
7	[80]	1	Trastuzumab	Preconception, 1	ER-/PR-/HER2+, metastatic	Ectopic pregnancy, elective abortion	-	-	-	-
8	[73]	1	Trastuzumab	Preconception, 1, 2, 3	ER-/PR-/HER2+, metastatic	Oligohydramnios	NI, W 32	1810 g	None	60 mo: ND
9	[81]	1	Trastuzumab	Preconception, 1, 2	NI, metastatic	Oligohydramnios, premature placental abruption	Section, W 27	NI	Decreased renal perfusion, renal dys-/hypoplasia, NRF	4 mo: death
10	[82]	1	Trastuzumab	Preconception, 1, 2, 3	ER+/PR-/HER2+, metastatic	Oligohydramnios, vaginal bleeding	Section, W 27	1015 g (57th P)	NRF, capillary leak syndrome, necrotising enterocolitis	21st week: Death due to MOF
11	[83]	1	Trastuzumab	Preconception	ER-/PR-/HER2+, metastatic	None	Section, W 39	3550 g	None	14 mo: ND
12	[84]	1	Trastuzumab + tamoxifen (+ methadone)	Preconception, 1, 2	ER+/HER2+, NI	Anhydramnios, premature rupture of membranes	Section, W 31 Twins	A: 1590 g B: 1705 g	A: NRF, renal failure B: transient NRF	A: 3 mo: Death due to respiratory failure
13	[85]	1	Trastuzumab	2	ER-/PR-/HER2+, metastatic	None	Section, W 29	1220 g	NRF	36 mo: ND
14	[85]	1	Trastuzumab	Preconception, 1	ER-/PR-/HER2+, not metastatic	2 gestational sacs with a viable foetus in only one of them	Vaginal, W 39	2940 g	None	24 mo: ND
15	[86]	1	Trastuzumab + tamoxifen + goserelin	2	ER+/PR-/HER2+, NI	Anhydramnios	Section, W 37	2690 g	Severe pulmonary hypoplasia, atelectasis	40 min: death
16	[87]	1	Trastuzumab	Preconception, 1, 2	ER-/PR-/HER2+, metastatic	Mother: Decrease in cardiac EF by up to 40%	Vaginal, W 37	3200 g	Mild transient tachypnoea	NI
17	[88]	1	Trastuzumab + carboplatin + docetaxel	2, 3	ER+/PR+/HER2+, not metastatic	Anhydramnios, foetal renal failure (W 21), IUGR	Section, W 34	NI	None	NI: ND
18	[89]	1	Trastuzumab (+ dexamethasone)	Preconception, 1, 2, 3	ER-/PR-/HER2+, metastatic	Oligohydramnios	Vaginal, W 37	3060 g	Transient tachypnoea	28 mo: ND

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► **Table 1** Trastuzumab for the treatment of PABC, overview of international case reports. (Continued)

No.	Reference	n	Therapeutic regimen	Trimester of exposure	Receptors/metastasis	Pregnancy complications/anomalies	Delivery	Birth weight	Neonatal status/complications	Follow-up children
19	[48]	16	Trastuzumab	Pregnancies which occurred during or up to 3 months after the administration of trastuzumab	HER2+, not metastatic	None	11 abortions (4 spontaneous, 7 elective), 5 live births: NI, W 40 on average	3485 g on average	None	NI, ND
20	[90]	1	Trastuzumab + vinorelbine	3	ER-/PR-/HER2+, metastatic	Anhydramnios	Section, W 33	1990 g	None	13 mo: ND
21	[91]	1	Trastuzumab + paclitaxel + dexamethasone + RT	2, 3	ER-/PR-/HER2+, metastatic	None	Section, W 38	NI	None	6 mo: ND
22	[92]	1	Trastuzumab	1, 2	NI, metastatic	Oligohydramnios (W 24)	Section, W 36	NI	None	3 Y: ND
23	[93]	1	Trastuzumab	1, 2	ER-/PR-/HER2+, not metastatic	Anhydramnios (W 28)	Section, W 32	1655 g	NRF, pulmonary infection	7 Y: ND

EF: Ejection fraction; IUGR: Intrauterine growth restriction; Y: Years; Mo: Months; MOF: Multiorgan failure; NI: Not indicated; ND: Normal development; NRF: Neonatal respiratory failure; P: Percentile; RT: Radiation therapy; Section: Caesarean section; W: Gestational week

Influence of the start of therapy

The data on the maternal outcome in breast cancer during pregnancy are not very comprehensive overall. In most studies, the success of treatment as well as the long-term prognoses of the affected children were primarily investigated. However, it can be said that there is presently a predominant consensus that pregnancy per se should not be considered to be an indicator for a worse prognosis of breast cancer. It was able to be demonstrated in several studies that pregnant breast cancer patients have a similar prognosis compared to non-pregnant women of the same age and tumour stage [2, 28–30]. Compared to non-pregnant patients, they are disproportionately frequently not diagnosed until an advanced tumour stage and for this reason, the outcome of these patients frequently appears to be worse overall [21, 49].

Based on this, it can thus be argued that postponing therapy in pregnant women would likely also have comparable negative effects as in the case of non-pregnant women. There is consensus that an existing pregnancy in general should not be a reason for postponing any indicated antineoplastic therapy [50]. Rather, the immediate introduction of therapy appropriate for the stage and tumour after diagnosis appears to be crucial for the outcome of the mother and, subsequently, also of the child, indirectly. Therefore any modifications to the recommended therapy to protect the unborn child should, if possible, be kept to a minimum.

However, it should also be noted at this point that this generally involves individual case-by-case decisions and the expectant mother's wishes should also be incorporated in the decision-making process [51]. HER2 inhibition with trastuzumab improves both progression-free survival as well as the overall survival in non-metastatic HER2-positive carcinomas as well as in stages which are already metastatic, and for this reason it can be assumed over-

all that postponing therapy for pregnant women, just as for non-pregnant women with comparable tumour characteristics, may have negative effects on these parameters [45, 52, 53].

Potential impact on the child

The concentration of a foreign substance which passes from the mother to the child largely depends on the placental transfer and, to a lesser extent, also on the placental as well as the foetal metabolism itself. The transplacental exchange of medicinal substances is affected by many factors. On the one hand, biochemical properties of the substance, such as the degree of ionisation, lipophilia, the degree of protein binding as well as the molecular weight, play a crucial role. On the other hand, the transfer is determined by characteristics relating to the placenta, such as blood flow, substance concentration gradients over the membrane, pH differences, an increasing exchange area with advancing pregnancy, or medicinal-product-metabolising enzymes which develop [54].

Most active substances overcome the placental barrier by means of passive diffusion. In this case, placental circulation, the pH difference between the mother's and child's blood as well as the biochemical substance properties and the degree of protein binding in each case represent in particular determining or limiting factors for the exchange substances [55, 56]. The facilitated diffusion as well as endocytosis are rarer means of transplacental medicinal substance transfer [57]. A paracellular exchange of substances, in particular of hydrophilic and charged substances via certain channel proteins, is possible [58–60].

By means of the mechanisms indicated, most drugs on the child's side of the placenta reach concentrations between 20 and 80% of the maternal concentration [61, 62]. However, the thick-

ness of the syncytiotrophoblasts continues to decrease with advancing pregnancy and also the cytotrophoblast, stromal and endothelial cells which follow become thinner and more permeable, and for this reason the exchange of substances between mother and child increasingly becomes easier [63].

Trastuzumab is a humanised monoclonal IgGk1 antibody [64]. Since immunoglobulins are large hydrophilic molecules with a molecular weight of about 150 kD, they overcome cell membranes via active transport by channel proteins [65]. The transplacental transport of IgG ultimately takes place via at least two membranes, that of the syncytiotrophoblast as well as that of the foetal capillary endothelium [63, 66].

HER2 receptors were identified in placental tissue in advanced pregnancy as well as in foetal renal tissue. As already described above, it is suspected that the interaction of trastuzumab with these receptors plays a role with regard to the more frequent occurrence of oligo- and anhydramnios on therapy [67]. The time of application of the antibody as well as the duration of therapy appear to have an influence here. Overall, a toxic effect of the active substance on foetal renal cells is considered to be the cause of the decrease in amniotic fluid. It is interesting that the amount of amniotic fluid increases once again after discontinuing the antibody and this is therefore a reversible effect. Growth factor receptors of the HER2 family which, as already mentioned, are expressed to an increased degree in human nephrocytes during the foetal period, induce DNA synthesis processes and promote cell division. In experimental studies as well, it was able to be shown that a blockade of these receptors led to decreased division activity of the nephrogenic cells [68–70]. That trastuzumab causes damage to foetal renal cells but not, however, maternal renal cells or adult renal cells is very likely due to the different protein structure of the growth receptor factor. This is therefore present in foetal renal cells as heterodimers, while in adults, it has developed in the form of a homodimer [71].

Moreover, trastuzumab is also involved in foetal neuronal and myocardial development. To date, however, no case of damage on trastuzumab to the paediatric nervous system or heart has been reported [72].

Conclusion

Numerous applications of trastuzumab were documented and the corresponding cases were published. Several low-complication pregnancies but also significant adverse effects were seen in some cases, and thus a general recommendation for use in pregnancy still cannot initially be made. Therefore a decision should be made in individual cases by a team of experts as to whether trastuzumab therapy is indicated.

Oligo- or anhydramnios occurs comparatively frequently during therapy. Interestingly, the amount of amniotic fluid increases once again after the antibody is stopped. This effect thus appears to be reversible. A toxic effect on the renal cells of the child is therefore presumed [68]. To date, the molecular mechanism by which trastuzumab causes a decrease in amniotic fluid has not been able to be clarified, however there are hypotheses which refer to the involvement of epidermal growth factor receptors in foetal tissue [73].

Growth factors of the HER2 family are expressed to an increased degree in human nephrocytes during the foetal period. They induce DNA synthesis processes there and promote cell division. In experimental studies, it was able to be shown that a blockade of these receptors led to decreased division activity of the nephrogenic cells. Similarly, trastuzumab could play a role in the HER2 blockade [69, 70]. In addition, HER2 is also involved in foetal neuronal and myocardial development. To date, no case of damage to the paediatric nervous system or heart on trastuzumab is known, however this potential risk should not be disregarded. In the case of administration of anthracyclines and the subsequent administration of trastuzumab, caution is called for in particular with regard to possible adverse cardiotoxic effects [74].

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Conflict of Interest

The authors declare that they have no conflict of interest.

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