Trastuzumab treatment for breast cancer during pregnancy

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ABSTRACT

QUESTION One of my patients has been diagnosed with breast cancer and started treatment with trastuzumab. She has recently discovered that she is pregnant and wishes to continue the pregnancy. What are the consequences of trastuzumab treatment during pregnancy and can she continue her pregnancy?

ANSWER Human data regarding the safety of trastuzumab during pregnancy are scarce. Only 3 case reports could be located in the published literature. Anhydramnios was observed in a case where the exposure to trastuzumab occurred during the second trimester, which reversed after discontinuation of the drug without any apparent consequences to the baby. Evidence is insufficient to provide any recommendations, but in light of the case reports, pregnancies exposed to trastuzumab during the second trimester should be closely followed with particular attention to amniotic fluid volume.

RÉSUMÉ

QUESTION Une de mes patientes a reçu un diagnostic de cancer du sein et a commencé un traitement au trastuzumab. Elle s'est récemment rendu compte qu'elle était enceinte et souhaite poursuivre sa grossesse. Quelles sont les conséquences d'un traitement au trastuzumab durant la grossesse, et peut-elle continuer cette grossesse?

RÉPONSE Les données chez l'humain concernant l'innocuité du trastuzumab durant la grossesse sont rares. Nous n'avons pu trouver que 3 rapports de cas dans les ouvrages publiés. Un cas d'anhydramnios a été observé après l'exposition au trastuzumab durant le deuxième trimestre, qui s'est réglé après avoir discontinué le traitement, sans conséquence apparente pour l'enfant. Les données scientifiques sont insuffisantes pour donner une quelconque recommandation mais, à la lumière des rapports de cas, il faudrait suivre de près toute grossesse pendant laquelle une femme est exposée au trastuzumab durant le deuxième trimestre et accorder une attention particulière au volume de liquide amniotique.

The management of breast cancer during pregnancy is a complex clinical issue because of the potential risks to the fetus posed by cancer treatment clashing with the potential risks to the mother from delayed cancer treatment.

Trastuzumab is a monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2) protein. The HER2 protein is a member of the epidermal growth factor receptor family. When the HER2 protein is overexpressed, it causes increased cell growth and proliferation leading to a more aggressive breast cancer. Treatment with trastuzumab has been shown to improve outcomes in the treatment of HER2-positive breast cancer.[1] This drug is listed as a category-B drug by the United States Food and Drug Administration. There is no similar classification system in Canada.

Animal data

According to the manufacturer of trastuzumab,[2] reproduction studies in monkeys have been conducted at doses up to 25 times the weekly human dose of 2 mg/kg. No decrease in fertility or fetal harm was noted. Transfer of the antibody in milk was observed, although there were no detected adverse effects in the offspring.

Although these data are reassuring, the epidermal growth factor receptor seems to be important in fetal development. The role of the mouse epidermal growth factor receptor 2 in development was investigated by Lee at al[3] in mice carrying a null allele. They reported high mortality of the mutant embryos, probably as a result of dysfunctions associated with a lack of cardiac trabeculae. Development of cranial neural crest–derived sensory ganglia was also markedly affected, as well as the development of motor nerves.

Human data

Published human data are very scarce. Only 3 case reports could be located in the literature. Watson[4] reported a case of a patient with breast cancer who was treated with trastuzumab during pregnancy. Results of an ultrasound study at 23 weeks' gestation indicated symmetric fetal growth, biometry consistent with

gestational age, and lack of amniotic fluid (anhydramnios). The fetal kidneys appeared in the ultrasound and seemed normal in size and echogenicity. The fetal bladder was small, and there was no change in bladder size noted during a 20-minute examination, an indicator of reduced urine production.

Anhydramnios in this case resolved slowly after the drug was discontinued. Labour was induced at 37 weeks and resulted in vaginal delivery of a healthy baby with normal renal function and no evidence of pulmonary hypoplasia or other complications commonly associated with anhydramnios.

Fanale et al[5] described the successful treatment of a woman at 27 weeks of pregnancy with recurrent HER2-overexpressing breast cancer who was symptomatic from multiple liver metastases. The chemotherapy regimen included trastuzumab injections. They reported complete resolution of the disease and delivery of a healthy male infant at 34 weeks' gestation. No oligohydramnios was reported.

Waterston and Graham[6] reported on a case of a 30-year-old woman who developed breast cancer and became pregnant while undergoing treatment with trastuzumab. She received a loading dose then an additional dose 3 weeks later. Just before her third cycle of trastuzumab, she had a positive pregnancy test result and could identify her conception date as 3 days after her second cycle of trastuzumab. Owing to her pregnancy, she chose to withdraw from the treatment and was monitored closely by the oncology and obstetric team. She successfully gave birth to a female baby, at term, by spontaneous vaginal delivery with no sequelae. No malformations were reported.

Conclusion

Information regarding human exposure to trastuzumab during pregnancy is limited to several case reports, none of which observed malformations, although 1 had anhydramnios. Women treated with trastuzumab should be closely monitored by ultrasound for fetal well-being in general and for volume of amniotic fluid in particular, in light of the report by Watson.[4]

Evaluation of the mechanism of action of the HER2 protein in fetal development is required and might further our understanding of safety and treatment options during pregnancy.

Clinicians who care for breast cancer patients treated with trastuzumab during pregnancy are encouraged to report their experience in order to provide others with evidence to guide their practice.

References

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MOTHERISK

Motherisk questions are prepared by the Motherisk Team at the Hospital for Sick Children in Toronto, Ont. **Dr Shrim** and **Dr Garcia-Bournissen** are members and **Dr Koren** is Director of the Motherisk Program. **Dr Shrim**, **Dr Maxwell**, and **Dr Farine** work in the Maternal Fetal Medicine Unit at Mt Sinai Hospital in Toronto. **Dr Koren** is supported by the Research Leadership for Better Pharmacotherapy during Pregnancy and Lactation and, in part, by a grant from the Canadian Institutes of Health Research. He holds the Ivey Chair in Molecular Toxicology at the University of Western Ontario in London.

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