ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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Safety of Chemotherapy in Pregnancy

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H&O Traditionally, what has been the approach to administration of chemotherapy during pregnancy?

FA Physicians were reluctant to give chemotherapy during pregnancy because the long-term safety outcome was uncertain, especially with regard to the child. The prognosis was thought to be better when pregnancy was interrupted. Avoidance of chemotherapy during pregnancy resulted in 3 situations. First, there were terminations of pregnancy. Second, maternal treatment was delayed until the baby was viable. After the baby was born, the mother would then start the chemotherapy. Third, physicians might choose not to start chemotherapy during pregnancy and then induce labor early, so that chemotherapy could be started after delivery. In my experience, the long-term consequences of prematurity have long been underestimated. The interdisciplinary teams that decided on the course of management usually included oncologists, surgeons, and gynecologists; obstetricians and perinatologists were generally not consulted. A decision might be made to induce delivery at 32 weeks, when the baby was thought to be viable. However, even at 32 weeks, there may be important long-term consequences of premature delivery.

H&O What prompted your recent study on long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy?

FA The study was prompted by a patient I treated in 2004. I was trained as an obstetrician; my focus on gynecologic oncology came later. This patient had cervical cancer, and she was pregnant. She had been advised to terminate the pregnancy and eventually undergo hysterectomy. She had lost her first pregnancy at 20 weeks due to a premature rupture of the membrane. She considered this second pregnancy her last chance to have a baby of her own.

My colleagues and I started examining the literature, and we saw only gaps in knowledge. There was very little research. There were no data on transplacental passage of chemotherapy. There were no data on pharmacokinetics. There was not a single report that examined outcome in children born to women who had received chemotherapy. This large gap in scientific knowledge, which was clinically very relevant, prompted the research.

H&O What was the study design?

FA The study was both retrospective and prospective. For the prospective arm, we followed children who were antenatally exposed to radiotherapy or chemotherapy to predefined ages. The children were first examined neonatally. At 18 months, we administered the Bayley Scales of Infant Development to test cognitive function. Thereafter, the patients underwent annual testing until they reached age 18. We assessed their intelligence, attention span, and behavior. We also performed detailed cardiographic evaluations. The parents completed questionnaires regarding the children's behavior and general health.

For the retrospective arm, we identified women who had received chemotherapy during pregnancy and given birth. We contacted these women and asked if we could examine their children according to our protocol. An advantage to this retrospective strategy is that it provided immediate long-term follow-up.

H&O What were the study findings?

FA We recently published the results of an interim analysis in *Lancet Oncology*. We found that children exposed prenatally to chemotherapy performed as well as other children from the same age group. What was striking is that the children who did not do well were more likely to be born prematurely. The main finding of the study is that prematurity corresponds to a worse cognitive outcome. We calculated that for every week that a child remains with the mother, his or her IQ score increases by 2.5 points. Those children in the study who did not do well were more likely to be born prematurely. Our conclusion is that children probably suffer more from premature delivery than from chemotherapy. Chemotherapy might be a means to prolong pregnancy until the baby is mature.

Heart function was also normal, even in children who were exposed to anthracyclines, which are notorious for their cardiotoxic effects. I should mention that there was 1 twin pregnancy, and these children did poorly. They were not able to take the attention and behavioral tests. We hypothesized that their clinical picture is one of a syndrome, which is not likely to be induced by chemotherapy.

The study has 3 limitations. The study design did not include controls for the neurocognitive and behavioral tests; those results were compared with normal values. A total of 70 children were included in the study, and ideally that number would be higher. In addition, the median follow-up of 22 months would ideally be longer. However, this follow-up is the longest that has been published until now, and, in my experience, normal test results at 22 months are predictive of normal outcomes at later ages.

H&O What are the implications of your study findings?

FA Our study suggests that chemotherapy is not associated with detrimental symptoms, such as congenital malformations or educational problems, so we hope that fear of chemotherapy during pregnancy will no longer lead to delay of maternal treatment, termination of pregnancy, or induction of preterm delivery in order to treat the mother with chemotherapy afterwards. We believe that chemotherapy can be given during pregnancy without delay and for 35 weeks. The goal is to deliver a full-term baby. I acknowledge that this outcome will not always be possible, but the goal might be part of a new strategy.

H&O Are you conducting any other research in this field?

FA In our laboratory, we are focusing on the transplacental passage of chemotherapy and combinations of chemotherapy. We are looking at larger groups with longer follow-up and are gathering data for a control group. We have a special emphasis on breast cancer, which is the most common cancer during pregnancy and accounts for approximately 40% of cases, followed by blood cancers (20%). These cancers are also the most common among all women during their reproductive years; pregnancy itself is not a risk factor for a particular cancer.

We have a task force within the European Society of Gynecological Oncology (ESGO). The website www.cancerinpregnancy.org provides information for patients and clinicians, as well as access to a registration study. We would like to collaborate with researchers internationally. The use of chemotherapy in pregnancy is not very common, and we would like to pool the small numbers generated at individual centers to a larger data set.

Suggested Readings

Amant F, Van Calsteren K, Halaska MJ, et al. Long-term cognitive and cardiac outcomes after prenatal exposure to chemotherapy in children aged 18 months or older: an observational study. *Lancet Oncol*. 2012;13:256-264.

Amant F, Loibl S, Neven P, Van Calsteren K. Breast cancer in pregnancy. *Lancet*. 2012;379:570-579.

Van Calsteren K, Heyns L, De Smet F, et al. Cancer during pregnancy: an analysis of 215 patients emphasizing the obstetrical and the neonatal outcomes. *J Clin Oncol*. 2010;28:683-699.