

Pregnancy Associated Breast Cancer: an Analysis of Fetal Treatment Risk
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Abstract

There are several viable treatment options for patients with PABC considered un-harmful to fetal development. Trastusumab, or Herceptin, targets HER2 protein and successfully combats aggressive breast cancer. In standard doses, it appears to be safe to the fetus even when administered during the first trimester. A likely side effect of Herceptin is anhydramnios, which can be monitored for throughout the stages of a pregnancy (Shrim et al. 2008). Anthracyclines, commonly used in chemotherapy, appear to be non-toxic, and have been used to successfully cure PABC patients in their second and third trimester. However, first trimester spontaneous abortions are documented to increase dramatically in anthracycline receiving PABC patients (Ring A. E. et al. 2005). Taxanes, such as paclitaxel, docetaxel, and vinorelbine, are microtubule agents that are highly active against breast cancer. As cytotoxic drugs they can possibly disrupt organogenesis and their administration should therefore be delayed until after the first trimester. Taxanes as well as anthracycline treatments should also be halted three weeks prior to delivery to prevent the occurrence of neutropenia, a decrease in white blood cells (neutrophil) that raises the risk of infection, and allow for regeneration of platelet count in the bloodstream (Mir O. et al 2008). Breast surgery can be safely performed at any point of a pregnancy although it is recommended to be postponed until after the first trimester. External beam radiation and hormone therapy are both documented to have negative effects on a developing fetus and therefore should not be considered as possible treatment options for PABC patients. In diagnosing and assessing PABC, ionizing radiation should be replaced by chest x-rays accompanied with proper shielding to protect the fetus. Sonograms appear to be more effective in diagnosing breast cancer than mammograms, because of the changes in pregnancy related breast density. Although PABC treatment is more complicated than standard breast cancer treatment, treatment during pregnancy has been proven to be a feasible and recommended option (Loibl S. et al. 2005).

Introduction

Pregnancy Associated Breast Cancer (PABC) presents a treatment plan quandary. The diagnosis appears to present a conflict between the mother and fetus' health. The challenge facing the health care provider is how to balance the mother's cancer care, with the fetus' pre-natal care. The aim of the physicians is to provide optimal treatment to the mother so as to maximize her chances of survival whilst minimizing risk to the fetus. This will often require an extensive healthcare group consisting of an OBGYN, a medical oncologist, radiation oncologist, pediatricians, and sometimes a breast surgeon. This complex scenario arises in approximately three percent of breast cancer cases. However, this statistic is likely to increase as women are increasingly delaying pregnancy until a later age (Ring A. E. et al 2005). It is therefore crucial to gain a clear understanding of this commonly misconceived situation.

It has generally been the public supposition that a woman with cancer who was found to

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be pregnant would have to choose: her life or her baby's. However, with the publication of many more case studies it has become evident that, at least in regard to breast cancer, this is not the case. It has been shown through controlled case studies that the prognosis for women who undergo voluntary abortion is not more favorable than for those women who continue their pregnancy (Gottlieb S. 1999). Analysis of the treatment options will support the recommended course of treatment to the highest possible standard despite the difficulties in the diagnosis and treatment of breast cancer.

The major difficulties in diagnosing breast cancer in a pregnant woman arise from the physiological changes that occur in the breast, and from the inability to use certain staging investigative procedures that are normally used in non-pregnant women. Mammograms have been shown to be relatively ineffectual in pregnant women because they are too hard to interpret due to the increased breast density in pre-menopausal and pregnant women. Therefore, sonography is more often the method of choice to diagnose PABC. There are also many routine staging investigations for breast cancer that use ionizing radiation, which should certainly not be used on a pregnant woman within the first trimester. In addition, not enough proof is available to support the safety of this technique for the fetus even during the later stages of pregnancy. Instead, chest X-rays are considered relatively safe in pregnancy when proper shielding is used (Ring A. E. et al 2005a).

Treatment for breast cancer is manifold. There are various options and each case must be individually assessed to design a treatment plan that will work. The basic care recommendations are breast surgery, radiation, systemic chemotherapy and other cytotoxic drugs, hormone therapy, and supportive care. Breast surgery may be performed throughout pregnancy, however, because there is a greater chance of spontaneous abortion within the first trimester. It is recommended that surgery be postponed until the second or third trimesters and that fetal activity be monitored throughout surgery. External beam radiation is contraindicated during pregnancy because of the serious risks associated with fetal exposure, such as mental retardation and other malformations. Hormone therapy should be postponed until after delivery, because defects have been seen in mice studies; there have been reports of Goldenhar's syndrome and of ambiguous genitalia in children born to women exposed to hormone therapies. Supportive care for anthracycline-based chemotherapy is safe after the first trimester (Loibl S. et al 2005). The use of systemic chemotherapy is dependent on the drug type and the trimester in which it is used. Research on cytotoxic drugs is ongoing and is mostly confined to case studies and individual case reports. There are several specific drugs that deserve further analysis. They are: Trastuzumab or Herceptin, anthracycline-based drugs such as the doxorubicin, cyclophosphamide, and fluorouracil combination, and taxanes or anti microtubule agents such as, docetaxel, paclitaxel, and vinorelbine.

Trastuzumab

Trastuzumab, generically also known as Herceptin, is an IgG1 monoclonal antibody that is directed against the 2(HER2)protein. The HER2 protein is a member of the epidermal growth factor receptor family. In recent years, researchers have found that in certain breast cancer cases this protein can be over expressed. When this occurs it causes increased cell growth and proliferation leading to a much more aggressive breast cancer. This type of cancer was considered one of the more fatal breast cancers until the advent of drugs like trastuzumab that target this protein. The drug has been shown to significantly improve outcomes in patients with

HER2-positive breast cancer (Shrim A. et al 2008). Because HER2 over-expression has been found in up to 35% of breast cancer cases in young patients (<35 years), it is probable that it will be concurrent with PABC. Therefore, trastuzumab may be necessary during pregnancy, and the risk factors must be analyzed.

Epidermal growth factor receptors seem to be important in fetal development. HER2 is expressed in embryofetal tissue. Therefore, it might be critical to fetal development. It has also already been demonstrated that transplacental transfer of maternal monoclonal IgG1 antibodies is possible. It is therefore reasonable to expect that trastuzumab might cross the placental barrier (Witzel I. D. et al 2007). In this regard, however, animal research has not exhibited any fetal harm. Reproduction studies were conducted in monkeys at 25 times the weekly human dose, and no decrease in fertility or fetal harm were noted. This study indicates that more research is required on the exact mechanism of action of the HER2 protein in fetal development (Shrim A et al 2008).

There are several reports of case studies where trastuzumab was part of the treatment in a pregnant breast cancer patient. With this particular drug, there does not seem to be increased harm to the fetus if it is administered during the first trimester. This conclusion is drawn from the case of a patient presenting with metastatic breast cancer who was treated with trastuzumab at normally recommended doses throughout the first 24 weeks of her pregnancy. She underwent a caesarean section at 37 weeks and was delivered of a healthy baby. However, in another case a woman received 25 cycles of trastuzumab before becoming pregnant, then nine more cycles during pregnancy, and in this case, the fetus was affected. Because the mother presented at 27 weeks pregnant with severe vaginal bleeding, the baby was delivered preterm at 28 weeks via caesarean section. The baby suffered several disorders and died 21 weeks later due to multiple organ failure. This second case does not specifically indicate that trastuzumab caused the irregularities in the fetus because they could be related purely to prematurity. However, in this case the drug dose to the mother was much higher, which could indicate that despite reassuring findings in other research, higher doses of the drug could affect fetal development and result in an impaired prognosis of the newborn.

Treatment after the first trimester does not appear to result in long term fetal harm. There are two case studies of women with metastatic breast cancer who underwent trastuzumab treatment during the second trimester and had no reports of any disorders. One woman was treated until 24 weeks gestation, and the other started treatment at 27 weeks gestation and delivered a healthy male at 34 weeks. The other case reports of women treated with the drug during the second or third trimesters all document a condition called anhydramnios, a lack of amniotic fluid. One patient was treated with trastuzumab until 23 weeks when anhydramnios was diagnosed, and treatment was discontinued. The anhydramnios resolved itself after discontinuation of the drug and a healthy baby was delivered at 37 weeks. Two other patients underwent trastuzumab treatment in their second and third trimesters and suffered anhydramnios. In one case the mother received treatment from her 26th week to her 32nd week when a caesarean section was performed. The baby showed signs of several dysfunctions, however these were probably related to its prematurity, and were resolved. The child's further development was normal. In the second case, a mother treated at weekly intervals until 35 weeks gestation when labor was induced, showed persistent anhydramnios throughout treatment. However, she was delivered of a healthy baby. It appears that trastuzumab treatment is possible during pregnancy

with close monitoring of the fetus, especially monitoring of fetal renal function and amniotic fluid volume (Witzel I. D. 2007).

Anthracycline Based Chemotherapeutic Drugs

Anthracyclines are a drug species that damage DNA through different mechanisms. One of these mechanisms is topoisomerase II α poisoning. Since topoisomerase is over-expressed in rapidly growing tissues, it can lead to poisoning which can cause severe damage to the embryo or fetus. However, only low concentrations of anthracyclines have been found in fetal tissues and their cytotoxic potential is unknown. Also, existing case research appears to prove that anthracycline use during pregnancy is not toxic to the fetus, especially when not used during the first trimester. Anthracyclines are one of the most used and effective types of chemotherapy for breast cancer patients, and it is therefore useful to understand their effect on the fetus. Anthracyclines such as commonly used doxorubicin do not easily cross the placenta because of their high molecular weight. They are also substrates of the P-gp, a placental drug-transporting glycoprotein. This glycoprotein is of great importance in limiting the fetal penetration of potentially harmful compounds. Indeed, it has been noted that after intravenous injection of anthracyclines only barely detectable concentrations can be found in the fetus (German N. et al 2003). It would appear that anthracyclines are not likely to be toxic, however specifically with anthracycline-based chemotherapy, like the combination previously mentioned, the date of administration has an effect on the risks to the fetus.

The first trimester of pregnancy is the time of organogenesis, and the fetus is therefore at its most susceptible. When chemotherapy is administered in the first few weeks of pregnancy there is a very high rate of spontaneous abortion. Throughout the rest of the first trimester there is still a chance of spontaneous abortion and there is the additional risk of fetal malformations. The risk of fetal malformations when chemotherapy is administered within the first trimester is up to 17% as opposed to 1.3% in the two subsequent trimesters. In two different studies three women treated during the first trimester all suffered spontaneous abortions. However, one woman in a study from the University of Texas M.D Anderson Cancer Center was treated at 11 weeks and experienced no apparent adverse effects. As a result of these significant risk factors to the fetus, chemotherapy is usually avoided during the first trimester (Ring A. E. et al 2005b).

Treatment with anthracycline-based chemotherapy in the second or third trimesters does not appear to increase the risk of malformations. There are three large case study series published about this treatment. In a U.K study 16 children of mothers exposed to anthracyclines showed no congenital malformations. In a French survey 18 children were identified as having been exposed and none of them presented malformations. The M.D Anderson series reported 23 children exposed none of whom had malformations. However, when the doxorubicin dose exceeds 70 mg/mg² per cycle it has been shown that risk of severe fetal toxicity increases 30 fold. There is also a specific risk of cardiotoxicity associated with anthracycline toxicity later in pregnancy, although this has not been observed in any case studies. While chemotherapy appears to be safe during the second and third trimesters, it is advisable to stop treatments at least three weeks prior to delivery, in order to prevent neonatal infection, neutropenia and to ensure that the mother's blood counts are optimal at delivery (German N. et al 2003).

Taxanes

Among emerging therapeutic options for breast cancer are antimicrotubule agents or taxanes such as paclitaxel, docetaxel, and vinorelbine. These drugs display a high activity against breast cancer, and it is therefore necessary to understand how they may be used in conjunction with pregnancy. Because these drugs are relatively new the available research is confined to case studies, some animal data and knowledge of the nature of the drug.

Paclitaxel, docetaxel, and vinorelbine are mainly metabolized by cytochrome P450 isoforms. Because the maturation of these cytochromes mostly occurs in the first weeks of neonatal life, fetus' cannot metabolize these drugs and would therefore be highly susceptible to their toxic effects if a transplacental transfer were to occur. These drugs would actually be expected to cross the placenta because they have a relatively low molecular weight and are highly lipophilic. However, they are highly bound to plasma proteins and plasma protein binding is increased during pregnancy, which would potentially lead to a decreased active fraction of these drugs. These drugs are also substrates for the Pgp which has been found in high expression in the placenta. The placental Pgp serves to protect the fetus from a broad range of xenobiotics. The placental Pgp therefore appears to reduce transplacental transfer of antimicrotubule agents, making their clinical use possible in the second and third trimesters (Mir O. et al 2008).

Animal studies have shown paclitaxel and docetaxel to be toxic to the fetus. This has not been evident in human case studies, although it is recommended to postpone the use of these cytotoxic drugs until after the first trimester. This is firstly, to prevent spontaneous abortion, and secondly, to prevent disruption of organogenesis which could lead to malformations (Ring A. E. et al 2005a).

There are four reports of PABC treated with Paclitaxel. The median maternal age in the reports is 36 years. Treatment was started during the second trimester in 3 cases and during the third in one case. There were no documented complications, and three out of the four patients underwent caesarean section with no reported malformations. In all cases there was a follow up with a median of 16 months, where all the children appeared healthy and normally functioning. However, in three cases, women treated with paclitaxel combination therapies in the last three weeks before delivery, exhibited mild anemia in two fetus' and one case of grade four neutropenia.

In a literature review study there were six reports of patients with breast carcinomas who were pregnant and treated with docetaxel. The median maternal age was 34.5 years and docetaxel was only administered by itself in one case. Treatment was initiated during the second trimester in three cases, and in the third trimester in three cases as well. One fetus developed hydrocephalia only before treatment with docetaxel, but remained stable thereafter. The child developed normally and was considered healthy at 28 months. In the other five cases no malformations were reported. All the offspring appeared healthy with a median follow-up of 17.5 months.

There were five identifiable cases of PABC treated with vinorelbine. Vinorelbine is generally associated with other cytotoxic drugs such as fluorouracil, cisplatin, or trastuzumab. The advantage of using vinorelbine is primarily its lower rate of side effects, which is especially a factor in pregnant women. The median maternal age of these five reported women was 32

years. The drug treatment was started in the second trimester in two cases and during the third trimester in three cases. There was no grade three or four maternal toxicity reported, and there were no fetal malformations. All the children were reported healthy at a 23 month median follow up (Mir O. et al 2008).

Researchers and medical practitioners have voiced the safety of using taxanes during the second and third trimesters of pregnancy based on the data available. It is agreed that the use of these cytotoxic drugs should be stopped for three weeks prior to delivery in order to prevent neutropenia, and to allow the mother's blood to regenerate its platelet counts. Further research and analysis is required to investigate the possibility of low birth weight being associated with the use of taxanes during pregnancy.

Conclusion

This area of study is an ongoing development and does indeed require much more investigative research. One of the principal problems standing in the way of a clearer understanding of placental transfer of drugs is the inability to ethically analyze live placental tissue. In order to observe and document the way in which these drugs react within the placental barrier one would need to inject the drug into the placental tissue: not a feasible option. When the placenta exits the uterus after delivery the tissue dies immediately, and the activity of the drug within its tissues would be totally different then when it is in its living state. This means that essentially all the understanding and chemical analysis of the way drugs pass through the placenta is conjecture. Furthermore, there is no way to test human subjects with increased doses of these drugs to observe their potential toxicity, and animal testing has given results that do not match human experience. Many women abort a pregnancy in the face of a serious diagnosis causes less real life cases to be analyzed.

This last reason is the principal impetus behind this paper. The ability to treat cancer during pregnancy is generally believed to be a modern, groundbreaking concept. In reality, the cases of women successfully cared for while they were pregnant date back to the 1970's. Yet still today, the public is just beginning to understand that one need not make that most painful of choices (Paul P. 2008). The situation presented by a breast cancer patient who is also pregnant and wishes to continue their pregnancy, is still unusually sensitive. The idea of harming a fetus to benefit the mother is difficult. The majority of women who do choose to continue their pregnancy, even today, generally do so because of religious beliefs, not because they think they and their babies will survive and be healthy. It is this public misconception that must be righted. Women should not be allowed to feel self-doubt or nervousness, because they are opting to be treated while continuing their pregnancy. Although research on breast cancer specifically is most extensive, based on its higher rate of correlation with pregnancy, the examples made in this field of cancer also apply to various other less documented cancers. It is crucial that further research and analysis, such as the ongoing study at the MD Anderson Cancer Center, continue and are publicized, so that unborn children need not be lost, and so that mothers should not be forced to make an impossible choice.

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