36 Chemotherapy in pregnancy

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INTRODUCTION

Fortunately, both the diagnosis of cancer during pregnancy and the diagnosis of pregnancy during the active treatment of a previously diagnosed cancer are rare occurrences, with cancer affecting approximately 1 in every 1000 pregnancies (1). However, with such a large population of females within the reproductive age range, the number of patients and providers having to face such difficult treatment decisions is not insignificant. Fortunately, there are a growing number of options besides pregnancy termination, based on an increasing understanding of the effects of various chemotherapeutic agents on the growing fetus, at different stages of development.

The cancers occurring most commonly in pregnancy include cancers of the breast, uterine cervix, ovary, colon, and the lymphomas (2). Alternatively, the cancers most likely to occur in a woman of reproductive age include thyroid cancer and cervical cancer. As more women are waiting until into their 30s and 40s to have children, age-dependent cancers occurring in pregnancy may be of increasing importance. Regardless of the type of cancer diagnosed, patients are often left with difficult choices. They frequently have the incorrect assumption that they cannot simultaneously make the decision to save their own life, while preserving the life and health of their unborn child. Naturally, a team of support staff and counselors should be available to work through these issues as patients are educated and decisions are made.

COMMON CANCERS IN PREGNANCY

Breast Cancer

It is estimated that breast cancer affects between 19 and 33 per 100,000 pregnancies (3–5). The pathologic distribution of these tumors appears to coincide with other young non-pregnant patients and is predominantly ductal invasive carcinoma (6). They tend to be less likely to be estrogen or progesterone receptor positive, and there are mixed data on whether the pregnant state alters the likelihood of Her-2/neu positivity (7,8). The prognosis for women with breast cancer diagnosed in pregnancy is similar to that of other nonpregnant young women (9,10).

Treatment for patients with breast cancer may include surgery, chemotherapy, and radiation. The use of radiation treatment is best avoided whenever possible at any time during pregnancy. Doses lower than 1Gy have been associated with increases in the rate of mental retardation and are most pronounced when the fetus is exposed in the first trimester (11). Surgery, however, is thought to be safe and can be performed at any time during the pregnancy. As with all cancers, it is generally preferred to wait until after 12 weeks of gestation to perform surgery, avoiding the coincident association with a spontaneous abortion.

The use of cytotoxic chemotherapy in pregnancy has been reported for a number of different tumor types. While most of these studies have a limited number of patients, the data would suggest that many of these agents are quite safe in pregnancy, particularly in the second and third trimesters. In breast cancer, the use of a combination of 5-fluorouracil (5-FU), doxorubicin, and cyclophosphamide was found to be without complication to the fetus or infant when given in the second or third trimester (12). Taxanes have been used to treat patients with breast cancer. However, published studies at this time are limited to a small number of case reports (13,14). Other drugs used to treat breast cancer include vinorelbine, capecitabine, gemcitabine, trastuzumab, and tamoxifen, many of which are discussed subsequently.

Cervical Cancer

Owing to the adoption of a revolutionary screening program, most cervical cancers are caught early. However, there are many women who either fail to participate in cervical cancer screening or are failed by the inherent false-negative rate of modern screening techniques. Indeed, as many as 40% of women diagnosed with cervical cancer are of childbearing age, with the incidence of cervical cancer in pregnancy estimated to be between 1.5 and 12 per 100,000 (5,15,16).

Surgical options for the treatment of women with cervical cancer include cold knife conization and extrafascial hysterectomy for microinvasive disease, and radical hysterectomy for more advanced stages. Although conization has been performed safely in pregnancy, it has also been associated with severe bleeding and preterm labor, and is generally discouraged (17). It may be appropriate to delay treatment until after the completion of pregnancy for patients with microinvasive disease. It is recommended that these patients then undergo cesarean section, with or without hysterectomy. Hysterectomy can be performed at the time of diagnosis with the fetus in utero if pregnancy termination is desired.

In cases where cervical cancer is diagnosed early in pregnancy and termination is not an acceptable option, investigators have described the use of neoadjuvant chemotherapy. Significant responses have been reported in some cases, with reductions in tumor volume, enabling both delays in delivery and effective postpartum treatments (18,19). Agents used include combinations of cisplatin with vincristine or bleomycin (19,20). Delays in definitive treatment of up to 32 weeks have been reported, with patients who have gone on to achieve surgical resection without further recurrence (21).

Ovarian Cancer

As the use of ultrasound has become exceedingly common in the evaluation of early pregnancies and is, in fact, the standard of care in the midtrimester, an increasing number of ovarian

masses are being incidentally discovered. Although the majority of these masses are benign, a reported 2% to 3% are found to be malignant (22). The estimated incidence of ovarian cancer is 7 to 8 per 100,000 pregnancies (22,23). If reasonable, it is best to delay the surgical evaluation of an adnexal mass until after the rate of spontaneous abortion has dropped and the pregnancy has become independent of the corpus luteum, with an optimal target window of 16 to 18 weeks of gestation. If the mass is found to be cancer on frozen section, then surgical staging and optimal cytoreduction can be performed without significant risks to the fetus.

Adjuvant chemotherapy for the treatment of ovarian cancer currently includes the use of a platinum and a taxane, such as carboplatin and paclitaxel. The use of a platinum with paclitaxel has been reported in pregnancy with normal growth and development in infants and children at follow-up (24,25).

Malignant Melanoma

Unlike most other cancers developing in pregnancy, transplacental spread of malignant melanoma from mother to fetus has been described (26). Treatment of early-stage lesions is focused on surgical excision and can be performed safely in pregnancy as described previously. It is now quite common to perform sentinel lymph node mapping on patients at risk of having regional metastasis. Overall, it is thought that the use of radioactive tracers in pregnancy exposes the fetus to a very low dose of radiation ($<0.5\text{cGy}$) and can be used safely (27). Alternatively, for lesions excised later in the pregnancy, lymph node mapping and excision can be delayed until the postpartum period.

For patients with distant metastatic spread of melanoma, the use of chemotherapy has not met with impressive results. Agents administered during pregnancy include dacarbazine, temozolomide, cisplatin, vinblastine, and interferon alpha2b (28,29).

Lymphoma

Lymphoma, including both Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), has been estimated to affect 8 to 16 per 100,000 pregnancies (5,30). Patients with NHL tend to have more aggressive histologic subtypes and advanced-stage disease. Staging for the pregnant patient with lymphoma may include history and physical examination, blood tests, bone marrow biopsies, and chest X-ray with abdominal shielding. Although CT scans are well below the levels that might be considered teratogenic, such scans may be replaced with ultrasound or MRI where appropriate.

The use of radiation in the treatment of lymphoma is fairly routine. Although for reasons discussed previously, it may be omitted in the treatment of a pregnant patient. Furthermore, pregnancy termination should be considered at least for the patient diagnosed with aggressive NHL in the first trimester, when immediate treatment is critical.

HL is commonly treated with regimens such as ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Other regimens include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone), the Stanford V protocol (mechlorethamine, doxorubicin, vinblastine, vincristine, bleomycin, etoposide, and prednisone), and MOPP (mechlorethamine, vincristine,

procarbazine and prednisone). Rituximab with combined chemotherapy has also been described (31).

Thyroid Cancer

While thyroid cancer is not the most commonly diagnosed malignancy occurring in pregnancy, it is more likely to be diagnosed during pregnancy because of its predilection for females of reproductive age. Imaging studies commonly used in the evaluation of a possible thyroid cancer include CT scans to evaluate both the extension of the tumor into adjacent tissues and the presence of cervical lymphadenopathy, and ultrasound, to delineate lesion size, and its cystic and solid characteristics. Fine-needle aspiration is of varying accuracy depending on histologic type, although it can generally be performed safely in pregnancy.

Surgery remains the most important treatment modality for patients with differentiated thyroid cancer, and total thyroidectomy is preferred to hemithyroidectomy (32). However, surgical timing must be weighed against risks to the fetus and the inherent and often coincidental rate of spontaneous miscarriage in the early trimester, as previously discussed. Unique to thyroidectomy, however, is the careful consideration of neurologic development in a fetus exposed to improper levels of thyroid hormone following complete removal of the thyroid. After about 18 weeks of gestation, fetal thyroid production begins, and the effects of a maternal thyroidectomy become less important. However, it should be noted that several retrospective studies have failed to demonstrate a significant difference in disease progression or outcomes for patients in whom thyroidectomy was delayed until after delivery, when compared with those performed during the second trimester (32). Radioactive iodine is a commonly used adjuvant therapy for patients with thyroid cancer. It is frequently given 3 to 6 months after thyroidectomy and is not recommended during pregnancy.

SYSTEMIC CHEMOTHERAPY

Introduction

The overall incidence of congenital malformations after the use of cytotoxic drugs during pregnancy has been reported to be approximately 3%, which does not differ significantly from the baseline risk of malformations in the general population of 2% to 3% (33). Naturally, the risk of exposure to the fetus from these agents differs depending on the stage of organogenesis, with the risk of malformations following the first-trimester exposure as high as 10% to 20%, in contrast to 1% to 3% for the second and third trimesters (34–36).

The pharmacokinetics of standard chemotherapies administered during pregnancy would be expected to depart from well-investigated standards due to changes in renal clearance, large increases in circulating blood volumes, lower serum albumin, and third spacing of many chemotherapeutic compounds into the amniotic fluid. Overall, drug clearances are higher, although there have been few studies that have investigated the differences in chemotherapy pharmacokinetics in pregnancy and it is thus unclear what proper dose adjustments are necessary in this population (37). Most chemotherapeutic compounds are lipid soluble and can easily cross the placenta. As a result, it is expected that the fetus or amniotic fluid will have a similar or even a higher

concentration of the drug, or its active metabolite, than that in the maternal circulation.

The risk of exposure to chemotherapy can be stratified based on the age of the gestation, with the greatest risk of physical defects coinciding with the exposure during the period of organogenesis, from 2 to 8 weeks. For practical purposes, most report on the timing of exposure as being based on the first, second, or third trimester. As noted previously, there is some suggestion that second-trimester exposure has been linked to low birth weight. Chemotherapy given in the third trimester can predictably cause side effects in the newborn, which are similar to that expected in the adult, such as neutropenia, anemia, and thrombocytopenia.

Taxanes

Taxanes, including agents such as paclitaxel, docetaxel, ortataxel, and tesetaxel, are compounds originally derived from the bark of yew trees. They affect their antineoplastic properties by stabilizing tubulin, which blocks the function of microtubules essential for cell division. These agents are considered first-line therapy for the treatment of many cancers including those of the lung, ovary, and breast.

In rabbit and rat studies, fetal exposure to both docetaxel and paclitaxel have been associated with an increase in intrauterine deaths, increased fetal resorption, reduced fetal weight, and delayed ossification. Human studies have been limited to a scant number of case reports. In one report, docetaxel, cisplatin, and gemcitabine were given to a patient in the first and second trimesters of an unrecognized pregnancy (38). A healthy infant was delivered by cesarean section at 33 weeks, without congenital malformations. Sood et al. reported on the use of paclitaxel and cisplatin in a patient diagnosed with stage IIIC ovarian cancer at 27 weeks. After surgical debulking, she was given three cycles of chemotherapy prior to delivery. The child was 30 months of age, at the time of the publication, without any known abnormalities or developmental delays (24). Morris et al. reported on a patient with recurrent metastatic breast cancer diagnosed at 29 weeks of gestation. She received a total of six cycles of weekly paclitaxel and delivered a normal infant by elective cesarean section at 38 weeks (39). Additionally, a normal infant was delivered after three 21-day cycles of docetaxel given to a patient diagnosed with recurrent breast cancer at 15 weeks of gestation (13). Other reports have further confirmed that taxanes can be used safely in the second and third trimesters of pregnancy without significant risk of fetal malformations (14,40,41).

Alkylating Agents

Alkylating agents include the subclass of nitrogen mustards, of which the compounds in most common use today include cyclophosphamide, ifosfamide, and melphalan, and chlorambucil. To exhibit their antineoplastic properties, many of these agents, such as cyclophosphamide, must be converted to an active metabolite in the liver. The compounds then attach to the alkyl groups in DNA, causing cross-linking between double-helix strands and preventing the uncoiling of DNA that is necessary for replication. Alkylating agents are used in several different tumor types including, but not limited to, breast cancer, NHL, chronic

lymphocytic leukemia, ovarian cancer, bone and soft-tissue sarcomas, and rhabdomyosarcomas.

Cyclophosphamide has been demonstrated to have significant absorption through the skin and mucous membranes, and great care should be taken by fertile women when administering this drug (42). Exposure to cyclophosphamide in the first trimester has been associated, in a small number of reports, with growth deficiency, developmental delay, cranio-synostosis, blepharophimosis, flat nasal bridge, abnormal ears, and distal limb defects including hypoplastic thumbs and oligodactyly (43). Zemlickis et al. reported on a patient with acute lymphocytic leukemia who received cyclophosphamide daily in the first trimester of a twin gestation (44). Interestingly, the male twin was diagnosed with papillary thyroid cancer at 11 years of age and neuroblastoma at 14 years of age. The female twin was unaffected. While no fetal deformities have been noted from exposure in the second and third trimesters, growth restriction, microcephaly, and neonatal pancytopenia have been described (45).

There have been several detailing the use of ifosfamide in the second and third trimesters, most commonly in multiagent combinations (46–48). No fetal anomalies have been noted and the infants appeared to be developing normally. One report, however, described the development of fetal growth restriction and anhydramnios after the first cycle of combination chemotherapy including ifosfamide, which was initiated in the second trimester for a maternal diagnosis of rhabdomyosarcoma of the face (49). The effects of ifosfamide given to humans during the first trimester are unknown. However, animal studies have demonstrated increased resorption and lethal anomalies when the drug has been given at high doses early in the pregnancy.

In animal studies, there has been some suggestion that there may be inheritable chromosomal aberrations caused by exposure of germ cells to chlorambucil and melphalan (50). In humans, cardiac and renal defects, including renal agenesis, have been reported with fetal exposure to chlorambucil in the first trimester (51,52). Still, others have described the use of chlorambucil throughout pregnancy with delivery of normal infants (51).

Platinum Agents

In a manner similar to the alkylating agents, platinum compounds, including among others cisplatin, carboplatin, and oxaliplatin, cross-link DNA and prevent uncoiling, however, without the use of an alkyl group. They have been described as being alkylating-like. They have been approved for the treatment of many cancers including those of the ovary, uterus, bladder, head and neck, esophagus, lung, lymphoma, leukemia, and choriocarcinoma. Representing one of the only reports of a platinum compound being administered in the first trimester, Li et al. described a single case of microphthalmos following the use of the Dartmouth regimen (dacarbazine, carmustine, cisplatin, and tamoxifen) to treat a patient with metastatic melanoma (53).

Tabata et al. reported on the use of carboplatin as a single agent for four cycles, with delivery of a normal infant at 33 weeks, who demonstrated normal development at 1 year (54). Another child exhibited normal development at 18 months following two cycles of single-agent carboplatin in the

treatment of stage III ovarian cancer diagnosed at 22 weeks of gestation (55). Carboplatin has also been combined with paclitaxel, resulting in normal development at 6 months of a child following three cycles of the combination prior to delivery (56). Mir et al. reviewed more than three dozen reports on the use of cisplatin or carboplatin, alone or in combination, to treat malignancies in the second and third trimesters (57). They report no fetal malformations in any patient treated with either compound when started after the first trimester, with the exception of one case of ventriculomegaly, diagnosed in a fetus in close proximity to chemotherapy administration.

Antimetabolites

Antimetabolites include methotrexate and 5-FU. Methotrexate, a folic acid antagonist, is indicated for use in the treatment of many cancers, including breast cancer, head and neck cancer, acute lymphocytic leukemia, NHL, bladder cancer, colorectal cancer, and gestational trophoblastic disease. It is an abortifacient and should not be given at any time during pregnancy. When given in the first trimester, this class of agents is associated with a constellation of severe fetal anomalies known as "aminopterin syndrome." The syndrome includes growth deficiency, patent cranial sutures, craniosynostosis, unusual skull shapes, dysmorphic facies, hydrocephalus, mental retardation, and skeletal defects (35).

There are few reports on the use of methotrexate in the second and third trimesters. One patient presented at 25 weeks of gestation with metastatic breast cancer and was treated with two cycles of doxorubicin, methotrexate, and vincristine prior to delivery of a female without anomalies, who was developing normally at 2 years (58). Nabers et al. reported on the use of methotrexate initiated at 27 weeks in a patient with choriocarcinoma metastatic to the lung, with a coincident normal pregnancy (59). Additionally, Ring et al. reported on 12 patients treated with cyclophosphamide, methotrexate, and fluorouracil in the second and third trimesters, with no adverse fetal outcomes (60).

Much like methotrexate, 5-FU, a pyrimidine analog, has been associated with multiple congenital abnormalities when it has been used during the first trimester, including radial dysplasia, absent digits, and hypoplasias of the lungs, aorta, esophagus, duodenum, and ureters (61). However, Berry et al. reported on 24 patients treated for breast cancer in pregnancy. They noted no fetal abnormalities or neonatal complications with the use of a combination of fluorouracil, doxorubicin, and cyclophosphamide (12). Fluorouracil is also used in topical form to treat conditions of the vulva and vagina. Several patients have been inadvertently treated with this preparation in the first trimester, without any report of deformities (62).

Antibiotics

The most common antineoplastic antibiotics include dactinomycin-D and bleomycin. The former exerts antitumor activity by inhibiting DNA synthesis and function, and promotes the accumulation of intracellular free radicals that further damage DNA. It is approved for the treatment of Wilms' tumor, rhabdomyosarcoma, germ cell tumors, gestational trophoblastic disease, and Ewing's sarcoma. Exposure of the fetus to this compound has been limited to a few case reports in

the second and third trimesters, resulting in intact infants with normal development (63–65).

Bleomycin is a peptide that binds to iron and creates oxygen free radicals, damaging DNA. It is indicated for cancers of the head and neck, squamous cell carcinomas of the skin, vulva, and cervix, germ cell tumors, HL, and NHL. As with dactinomycin-D, no case reports of malformations from the first-trimester exposure have been reported for this drug. Second- and third-trimester exposures have been associated with the delivery of infants without deformities, and normal development has been reported (66,67). Nantel et al. reported on the use of 12 weekly cycles of methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in the treatment of NHL in a patient. The patient went into preterm labor and delivered twins without congenital abnormalities (68). Another patient with an endodermal sinus tumor diagnosed at 18 weeks was treated with three cycles of cisplatin, vinblastine, and bleomycin and delivered a healthy infant without abnormalities at 31 weeks (69).

Nucleoside Analogs

Nucleoside analogs, including cytarabine and gemcitabine, exhibit their antineoplastic properties by causing incorporation of either the drug or its metabolite into DNA and terminating replication. Cytarabine is indicated in the treatment of multiple types of leukemias, as well as in leptomeningeal carcinomatosis. The compound has been associated with otic and auditory canal anomalies, digital anomalies, lobster claw hand, and lower limb defects (70,71). Unlike most other chemotherapies, cytarabine has been associated with in utero fetal death, when given in the later trimesters, and should be avoided in pregnancy altogether, when alternative agents are available (72).

Gemcitabine is indicated in the treatment of cancers of the ovary, pancreas, bladder, lung, and in sarcomas. There are little data regarding the intrapartum use of gemcitabine in the literature. Studies in mice have demonstrated teratogenicity including decreased fetal weight, cleft palate, and increased mortality (73). Kim et al. reported on a woman with non-small cell lung cancer, treated with palliative docetaxel, gemcitabine, and cisplatin from weeks 9 to 22 of an unrecognized pregnancy. A healthy infant was delivered at 33 weeks with no recognizable anomalies (38). Hematologic toxicity is commonly dose limiting and the compound should be used with caution toward the end of the third trimester. In the absence of more case reports, or perhaps a series of patients, other compounds might be considered prior to choosing gemcitabine during pregnancy.

Topoisomerase Inhibitors

Topoisomerase I and II are involved in the cleaving of DNA strands for the purpose of replication. Topoisomerase inhibitors bind to the DNA-topoisomerase complex and prevent the advancement of the replication fork. Topotecan and irinotecan are examples of compounds specific to topoisomerase I, while etoposide binds specifically to the topoisomerase II-DNA complex.

Both topotecan and irinotecan are derivatives from the *Camptotheca acuminata* tree. As with the nonpregnant population, the most pronounced maternal toxicity associated

with topotecan is myelosuppression. To date, there have been no human studies evaluating the teratogenicity of this compound, and unlike most other antineoplastic agents, there are no reports of any pregnant patients receiving this drug. However, animal studies have been concerning. At levels equivalent to human doses, topotecan has been associated with reduced fetal body weight, fetal demise, fetal resorption, and brain, skull, and vertebrae malformations. Most commonly, malformations of the eyes were noted, including microphthalmia, anophthalmia, retinal defects, and ectopic orbits. Granted, most fetal effects are seen by early pregnancy exposure, in the absence of any human data, it is not recommended that topotecan be used at any time during pregnancy.

Irinotecan has also demonstrated animal embryotoxicity at doses equivalent to recommended human levels. Teratogenic effects include visceral and skeletal abnormalities, as well as some external defects. Furthermore, rats administered irinotecan after organogenesis and through weaning had decreased learning ability and decreased fetal weights in the female offspring (74). Unlike topotecan, there has been a single report of the use of irinotecan in pregnancy. A 34-year-old patient was diagnosed with recurrent colon cancer, metastatic to a single ovary at 15 weeks of gestation. She underwent surgical resection and, starting at 18 weeks, was treated with 10 courses of 5-FU and irinotecan over the next 5 months. She delivered a healthy infant at 37 weeks, with no appreciated teratogenic or developmental effects at 4 months (75).

Unlike the topoisomerase I inhibitors, there are dozens of published reports detailing the use of etoposide in pregnancy. Many of these patients have been diagnosed with endodermal sinus tumors, although a variety of other tumors have also been treated with this agent in pregnancy (76). Animal studies have demonstrated multiple fetal abnormalities when the drug is administered during organogenesis, including fetal loss, exencephaly, encephalocele, hydrocephalus, gastroschisis, microphthalmia or anophthalmia, dextrocardia, and axial skeleton defects (77). Etoposide is most frequently given with other agents such as bleomycin and cisplatin (BEP), and the reports occurring in the pregnant patients are no exception. One fetus developed ventriculomegaly and the child now has cerebral atrophy following a single course of BEP (78). Another patient had two cycles of BEP starting at 18 weeks and delivered a normal infant during laparotomy for metastatic disease at 31 weeks. Yet another patient, diagnosed at 26 weeks of gestation with Burkitt's lymphoma, was treated with cyclophosphamide, vincristine, doxorubicin, cytarabine, etoposide, ifosfamide, mesna, and intrathecal cytarabine and delivered a healthy baby at 32 weeks (46). Another patient was treated with BEP at 26 weeks for a metastatic tumor of unknown primary. She developed septicemia and delivered prematurely. The infant has moderate sensorineural hearing loss (79). Several other reports describe the delivery of normal, healthy infants following etoposide administration.

Doxorubicin is indicated in the treatment of many cancers, including, but not limited to, breast cancer, HL, and NHL, soft-tissue sarcoma, ovarian cancer, lung cancer, bladder cancer, thyroid cancer, and gastric cancer. The drug is an

anthracycline antibiotic isolated from *Streptomyces* species. It intercalates into DNA, which inhibits DNA synthesis. Doxorubicin also inhibits transcription, by inhibiting DNA-dependent RNA polymerase, and the function of topoisomerase II. Myelosuppression is dose limiting, but both acute and chronic cardiotoxicity have been well described. When given in the first trimester, in combination with other agents, doxorubicin has been associated with imperforate anus, rectovaginal fistula, and microcephaly (80). In the largest series to date, Hahn et al. reported on the use of doxorubicin in combination with 5-FU, and cyclophosphamide in 57 pregnant women (81). They reported three congenital anomalies, including Down syndrome, clubfoot, and bilateral ureteral reflux. Several others have reported the use of doxorubicin alone or in combination with other therapies, starting as early as the second trimester, without obvious effects on the fetus. There have been no reports of fetal or infant cardiotoxicity associated with doxorubicin use in pregnancy (67,82,83).

Epirubicin is sometimes used instead of doxorubicin as it can have faster elimination and fewer side effects. It has been used in breast cancer, ovarian cancer, lymphomas, gastric cancer, and lung cancer. There have been a few larger series describing the use of epirubicin in pregnancy. Azim et al. described the second-trimester administration of either doxorubicin or epirubicin to a total of 3 and 23 patients, respectively (84). They reported two preterm deliveries, no fetal anomalies, and normal development in all children.

Vinca Alkaloids

Vincristine is a vinca alkaloid antimicrotubule agent derived from the periwinkle *Catharanthus roseus* plant. It is indicated for the treatment of choriocarcinoma, brain tumors, thyroid cancer, leukemia, lymphoma, sarcomas, and several other malignancies. As noted above, vincristine has been used in combination with bleomycin and other agents, delivering infants without abnormalities. Tewari et al. reported on the neoadjuvant treatment of cervical cancer with cisplatin and vincristine in two pregnant women, both of whom experienced significant reductions in tumor volume (19). No adverse fetal effects were noted. Bader et al. also reported on the use of cisplatin and vincristine in a patient for the neoadjuvant treatment of a cervical cancer beginning in the 23rd week of pregnancy (85). At 33 weeks, the patient then underwent a cesarean radical hysterectomy, delivering a normal infant. There have been some sporadic reports of atrial septal defects, renal hypoplasia, and pancytopenia following the use of vincristine in pregnancy (45,86,87). Several other authors have reported the successful use of vincristine, most frequently in combination with other agents, leading to the delivery and normal development of healthy infants (88,89).

Vinblastine is also a vinca alkaloid derived from the periwinkle plant. It is indicated for the treatment of HL and NHL, breast cancer, Kaposi's sarcoma, and renal cell carcinoma. It exerts its antitumor effect by inhibiting tubulin polymerization and disrupting microtubules during the M-phase of the cell cycle. As with most agents described here, animal studies in early pregnancy have demonstrated increased resorption, spontaneous abortion, and gross fetal abnormalities. However, some human studies have reported

no teratogenic effects from first-trimester exposure (90). At 18 weeks of gestation, a patient was diagnosed with an endodermal sinus tumor of the ovary, and following laparotomy, she received three courses of cisplatin, vinblastine, and bleomycin (69). She delivered a healthy and normal infant at 31 weeks. To date, there have been more than half a dozen other patients who have received vinblastine in combination regimens, followed by the delivery of normal, healthy infants (91,92).

Vinorelbine is a synthetic derivative of vinblastine. It is indicated in the treatment of non-small cell lung cancer, breast cancer, ovarian cancer, and HL. When administered to a patient with lung cancer from the 27th to 39th week of pregnancy, a healthy and normal infant resulted (93). Several other patients have reportedly received vinorelbine during pregnancy, with therapy being initiated between 15 and 29 weeks of gestation. In this setting, the drug has most commonly been administered as part of a combination of chemotherapies, being paired with 5-FU, cisplatin, or trastuzumab. All infants have been delivered without congenital abnormalities, had normal birth weights, and have been developing normally (94–96).

Biologic and Growth Factor Agents

Trastuzumab is an antibody indicated for the treatment of patients with HER2 overproducing breast cancers. The antibody exerts its effect on cancer cells both by activating the body's immune response against the cells and by shutting down the signal that tells the cancer cells to grow and divide uncontrollably. Trastuzumab was given to six pregnant patients for the treatment of breast cancer. Anhydramnios developed in three out of the six patients treated (97). Another patient with recurrent metastatic breast cancer was treated with trastuzumab for the first 23 weeks of an undiagnosed pregnancy (98). The patient was delivered by cesarean section at 27 weeks due to severe vaginal bleeding. This pregnancy was also noted to have oligohydramnios. The infant was noted to have uncommonly strong capillary leak syndrome, persisting infections, and necrotizing enterocolitis. The baby died due to multiple organ failure 21 weeks after delivery. Other patients have received trastuzumab in the second and third trimesters without complication to the fetus (96).

Bevacizumab inhibits tumor angiogenesis by binding directly to vascular endothelial growth factor (VEGF). It is currently indicated for the treatment of glioblastoma, renal cell carcinoma, breast cancer, lung cancer, and colon cancer. Rabbit studies at human doses have demonstrated teratogenicity including gross and skeletal malformations, as well as low fetal body weights and increased resorption. Reports on the use of this compound in human pregnancies are very limited. Petrou et al. described two early pregnancy losses at 6 weeks of gestation 7 and 10 days following intravitreal injection of bevacizumab (99). Rosen et al., however, reported the use of the therapy in the second trimester without significant fetal effects (100).

Rituximab is a monoclonal antibody against CD20, which exerts its effect by selectively depleting CD20+ B cells. It is indicated in the use of rheumatoid arthritis and in lymphomas. Kimby et al. reported on the unintentional use of rituximab in

a patient with recurrent NHL in the first trimester of pregnancy (101). She delivered a normal, healthy infant without evidence of hematologic or immunologic abnormalities. Other reports of first-trimester administration have also demonstrated no teratogenic or immunologic effects on the fetus or neonate (102). Pellkofer et al. reported on the use of rituximab for the treatment of neuromyelitis optica 1 week prior to conception (103). The patient delivered a healthy infant with normal development at 15 months. Another patient with idiopathic thrombocytopenic purpura was treated with rituximab weekly for 4 weeks in the third trimester (104). A healthy infant was born 1 month after the last administration of the drug. However, the child had no detectable B lymphocytes. Six months following delivery, her B-lymphocyte counts were normal, and at 10 months, she had normal vaccination titers. Other authors have confirmed this finding of significant rituximab concentrations in the neonate, transient B-lymphocyte depletion, quick recovery, and an absence of immunologic or other neonatal consequences (105–107).

Imatinib is a specific inhibitor of a number of tyrosine kinase enzymes and is indicated for the treatment of chronic myelogenous leukemia. It has been associated with a high rate of teratogenicity (108). However, Skoumalova et al. reported on its administration throughout the first trimester of pregnancy, followed by the use of interferon for the remainder of the gestation, with the delivery of a normal and healthy child (108). Neither the drug nor its active metabolite appears to cross the placenta in significant concentrations (109). Nonetheless, Pye et al. reported on the evaluation of 125 pregnancies complicated by the use of imatinib (110). They reported that 3 of the 35 patients who terminated their pregnancies did so because of detected fetal malformations. Of the remaining infants delivered, 12 had malformations, and 3 of them had similar complex malformations including renal and vertebral anomalies.

Sunitinib is an oral inhibitor of multiple receptor tyrosine kinases including VEGF receptors. It is indicated for the treatment of refractory metastatic renal cell carcinoma and gastrointestinal stromal tumors. Rats and rabbits were given the drug during the periods of organogenesis and demonstrated malformations including thoracic and lumbar vertebral alterations, cleft lip and palate, and increased resorption (111). To date, there have been no reports of this drug administered during a human pregnancy.

Several interferon compounds have now been developed and marketed for the treatment of many kinds of diseases and malignancies. A thorough discussion of the fetal and neonatal effects of each of these drugs is beyond the scope of this chapter. However, there have been several reviews and case reports suggesting that interferon alpha appears to be associated with the delivery of normal and healthy infants (112–114). Mubarak et al. reported on the use of interferon alpha for the treatment of chronic myeloid leukemia beginning in the first trimester (115). Although one child was born with transient thrombocytopenia, all three infants were without abnormalities and developing appropriately. It should be noted that there have been reports of maternal postpartum cardiomyopathy developing in women who have been treated with interferon prior to pregnancy (116).

Birth Weights, Development, and Long Term Follow Up

Some authors have suggested that birth weights for infants born to mothers with breast cancer were significantly lower than those of healthy controls (117). However, in one of the largest series to date, Aviles et al. reported on the long-term follow-up of 84 children and grandchildren of patients treated with chemotherapy for hematologic malignancies during pregnancy (118). The median follow-up was 18 years and ranged from 6 to 29 years. They reported normal birth weights, normal learning and educational performance, no congenital abnormalities, and no cancer or leukemia, with a median follow-up of 18 years and a range of 6 to 29 years.

Infant Hemotoxicities

Some authors suggest that patients should not be treated after 35 weeks of gestation, as many infants may be born with neutropenia, thrombocytopenia, and profound anemia under these circumstances (117). Indeed, infants have been born with severe anemia requiring prolonged ICU admissions, following chemotherapy administered during pregnancy (119). Progenitor studies in these infants have revealed severe bone marrow suppression. Infants should be monitored following delivery for such effects for a prolonged period of time.

SUMMARY

With such a large and growing population of women of reproductive range, the absolute number of women who will be diagnosed with a pregnancy during cancer treatment or diagnosed with a cancer during the course of her pregnancy is far from negligible. The contrast that can occur when the happiest time in a woman's young life is shattered by the finding of often metastatic disease is universally devastating for the patient, her family, and all of those who are involved with her care. Significant moral and ethical dilemmas arise, and questions regarding teratogenicity, pregnancy termination, and disease prognosis have to be approached and considered by a team of physicians, nurses, social workers, counselors, and loved ones. Fortunately, it is clear that there are a number of such malignancies that are curable, and it is further understood that most chemotherapies can be well tolerated in the second and third trimesters without effects on the fetus or on the future development of the child.

With a growing number of chemotherapeutic compounds available, and at least some differences among their effects in pregnancy, multiagent and single-agent combinations should be custom-tailored to provide patients with the best possible treatment of their neoplasm, while exposing the fetus to the least teratogenic, growth restricting, and hemotoxic regimens. Fortunately, it is evident that at least some patients will emerge from this difficult situation disease free and raise healthy and developmentally normal children.

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