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Review Article

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Review Article

Anticancer drugs during pregnancy

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Abstract

Although cancer diagnoses during pregnancy are rare, they have been increasing with the rise in maternal age and are now a topic of international concern. In some cases, the administration of chemotherapy is unavoidable, though there is a relative paucity of evidence regarding the administration of anticancer drugs during pregnancy. As more cases have gradually accumulated and further research has been conducted, we are beginning to elucidate the appropriate timing for the administration of chemotherapy, the regimens that can be administered with relative safety, various drug options and the effects of these drugs on both the mother and fetus. However, new challenges have arisen, such as the effects of novel anticancer drugs and the desire to bear children during chemotherapy. In this review, we outline the effects of administering cytotoxic anticancer drugs and molecular targeted drugs to pregnant women on both the mother and fetus, as well as the issues regarding patients who desire to bear children while being treated with anticancer drugs.

Key words: anticancer drugs, pregnancy, malformation

Introduction

Maternal age has risen in many developed countries and as cancer morbidity increases with age, the number of women diagnosed with cancer during pregnancy is also growing. Cancer is detected at a frequency of approximately one in every 1000 women during pregnancy, the most frequent being breast cancer, cervical cancer, malignant lymphoma and malignant melanoma (1).

There are some cases of cancer diagnosed in pregnant women in which the administration of chemotherapy is unavoidable; however, there is limited evidence for the effects of administering chemotherapy. We assume that the primary reason is that performing clinical trials is extremely challenging from an ethical perspective because there are concerns regarding the effects of the anticancer drugs on the fetus.

The package inserts of several anticancer drugs state that administration during pregnancy is contraindicated, contraindicated as a general rule or that chemotherapy can be administered if the benefits of treatment outweigh the risks (Table 1). Since there is a lack of evidence for the administration of anticancer drugs during pregnancy, it is challenging to know on what basis we should discuss the possible benefits after explaining the risks to pregnant women being assessed as to whether chemotherapy should be administered. Unless it is a major facility where medical oncologists, hematologists and obstetricians can cooperate closely for the patient's sake, in principle no anticancer drugs should be administered.

Congenital malformations can occur in approximately 20% of cases if chemotherapy using cytotoxic anticancer drugs is administered during the first trimester and thus should be avoided (2). However, from the second trimester onwards, if sufficient consideration is given to the safety and long-term effects of the mother and fetus and if it is determined that chemotherapy is required, then chemotherapy that can be administered has also been reported in previous observational studies. In addition, there are limited numbers of case reports regarding the use of molecular targeted therapy for pregnant cancer patients. Recently, international guidelines have also been published, indicating that this issue has become one of major international concern (3,4).

In this paper, we review the effects of the main anticancer drugs and molecular targeted agents on the mother and fetus during

Table 1. The risks to the fetus when administering anticancer drugs to pregnant women in Japan (according to the package insert for each drug)

	Contraindication	Contraindicated in principle	Administered if the benefits of the treatment outweigh the risks	Should not be administered
Cytotoxic agents	Paclitaxel (D) Docetaxel (D) Dacarbazine (C) Methotrexate (oral) (X) Carboplatin (D) Cisplatin (D)			Doxorubicin (D) Epirubicin (D) Daunorubicin (D) Idarubicin (D) Cyclophosphamide (D) 5-FU (D) Methotrexate (iv) (X) Cytarabine (D) Vinblastine (D) Vincristine (D)
Hormonal agent	Tamoxifen (D)			
Molecular targeted agents	Pertuzumab (D) T-DM1 (D) Lapatinib (D) Imatinib (D) Sunitinib (D) Sorafenib (D) Bevacizumab (C)	Gefitinib	Trastuzumab (D) Erlotnib (D) Cetuximab (C) Panitumumab (C) Rituximab (C)	

Risks according to the FDA in brackets:
C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.

pregnancy. Furthermore, we explore the issues surrounding anticancer drug administration in patients who desire to bear a child.

General considerations

When administering chemotherapy during pregnancy, the extremely difficult issue of providing maximum treatment benefit to the mother while maintaining the safety of the fetus must be addressed.

Adverse effects from any drug on the fetus are also thought to be affected by the timing of exposure to the drug, dose and placental transfer of the drug. Drugs with high lipid solubility, low-molecular weight and a low plasma protein-binding rate have a higher placental transfer (Tables 2 and 3) (5). There are ethical difficulties regarding performing research on the placental transfer of anticancer drugs in human subjects and therefore, in most cases, data have been achieved using animal experiments. In many cases, the placenta inhibits or attenuates the passage of drugs through various mechanisms (6). For example, p-glycoprotein, which is strongly expressed in the human placenta, may attenuate the placental transfer of taxanes (7).

Even if chemotherapy is initiated from the second trimester onwards to avoid congenital malformations caused by anticancer drugs, the risks of intrauterine growth retardation (IUGR), premature rupture of membranes (PROM) and premature labor are still increased (20–22). For this reason, fetal monitoring during each chemotherapy cycle throughout pregnancy is appropriate. In addition, if chemotherapy is administered during pregnancy, the rate of preterm delivery increases and, although negligible, delays in neonatal cognitive development have been identified. Therefore, it is recommended that delivery should be at 37 weeks or later, if possible (3,23). However, some physicians are of the opinion that the infant should be delivered slightly earlier in order to adequately treat the mother. The delivery period in actual clinical practice is highly controversial and greatly depends upon the condition of the mother and fetus as well as the type of cancer. Therefore, a thorough deliberation between the obstetrician, oncologist and pediatrician is vital.

Chemotherapy should not be administered from Week 35 onwards, or within 3 weeks of the scheduled delivery date, to avoid the risk of hematological complications during delivery (24). Regimens administered on a weekly basis (e.g. those for doxorubicin, epirubicin and paclitaxel) demonstrate low hematological toxicity. However, if chemotherapy is administered up until immediately before delivery, it may affect the neonate, who retains only a limited ability to metabolize drugs after delivery. Therefore, this should be avoided. In addition, the presence of placental cancer metastases must always be assessed after delivery and, if chemotherapy is required after delivery, breastfeeding must be avoided (6).

In terms of the effects of cancer treatment prior to delivery on children, reports have found no differences regarding general and cognitive development, and cardiac function in early childhood (25). However, there are few studies involving long-term observation and the possibility of late-onset effects (e.g. cardiomyopathy, abnormal reproductive function, drug-induced onset of cancer and psychomotor retardation) remains unknown.

Cytotoxic agents

In women who received chemotherapy during pregnancy, the rate of congenital malformation in the fetuses is approximately 5%. However, the majority of cases received chemotherapy during the first trimester; the rate of these malformations occurring in those receiving chemotherapy from the second trimester onward is 3%, which is the same as the percentage of fetuses observed to have congenital morphological abnormalities in normal pregnancies (8,26). Furthermore, reports indicate that spontaneous abortion occurs in approximately 15% of patients receiving chemotherapy (8,26).

The complications of chemotherapy during pregnancy often include oligohydramnios and IUGR, but preeclampsia and PROM may also occur. Approximately one-third of all cases deliver early, with many deliveries via cesarean section, and an increased

Table 2. Effects of cytotoxic anticancer drugs on the fetus and their characteristics

Drug		Fetal/maternal drug concentration ratio	Method	Major malformation (8)		Small for gestational age[a] (8)
				During the first trimester	After second trimester	
Anthracycline antibiotics	Doxorubicin	7.5% (9)	Baboon plasma	13% (5/39)	2% (6/383)	6% (26/417)
	Epirubicin	4.0% (9)	Baboon plasma	20% (1/5)	5% (3/58)	5% (3/62)
Taxanes	Docetaxel	0% (10)	Baboon plasma	0% (0/2)	11% (2/19)	19% (4/21)
	Paclitaxel	1.5% (10)	Baboon plasma	—	3% (1/38)	13% (5/38)
Alkylating agent	Cyclophosphamide	25.1% (9)	Baboon plasma	18% (7/40)	1% (5/366)	7% (28/400)
	Dacarbazine	Unknown		11% (1/9)	2% (1/45)	13% (7/53)
Antimetabolites	Cytarabine	56.7% (11)	Mouse plasma	19% (4/21)	4% (4/109)	13% (17/131)
	5-FU	28.7% (12)	Rat plasma	31% (4/13)	2% (3/161)	6% (11/171)
Vinca alkaloids	Vinblastine	18.5% (9)	Baboon plasma	31% (5/16)	5% (3/57)	10% (8/80)
	Vincristine	Unknown		9% (4/44)	1% (1/159)	13% (25/199)
Platinum agents	Cisplatin	31–65% (13)	Human umbilical cord	20% (1/5)	4% (4/99)	13% (13/102)
	Carboplatin	57.5 (10)	Baboon plasma	—	6% (1/17)	13% (2/16)

[a]Small for gestational age was identified as body weights that were <10th percentile of the normal population based on sex and gestational age at birth or as reported by the authors when clearly defined.

Table 3. Effects of molecular targeted agents on the fetus and their characteristics

Drug		Fetal/maternal drug concentration ratio	Method	Dose	Time after the last administration	Major malformation (8)		Small for gestational age[a] (8)
						During the first trimester	After second trimester	
Monoclonal antibodies	Trastuzumab	85.0% (10) 3.0%	Baboon plasma	8 mg/kg	2 hours 26 hours	0% (0/12)	0% (0/6)	5% (1/19)
	Pertuzumab	30–40%[b]	Cynomolgus serum	10 mg/kg 33.3 mg/kg 100 mg/kg	50 days	—	—	—
	Bevacizumab	2–9% (14)	Rabbit serum	10 mg/kg 100 mg/kg	3 days	—	—	—
	Rituximab	328% (15)	Human cord blood serum	375 mg/m^2	3 months	20% (1/5)	0% (0/18)	5% (1/23)
		150% (16)	Human neonatal blood serum	375 mg/m^2	2 months			
Tyrosine kinase inhibitors	Gefitinib	20% (17)	Human cord blood	250 mg/m^2	16.5 hours	0% (0/2)	0% (0/4)	66% (4/6)
	Erlotinib	25% (18)	Human cord blood	150 mg/m^2	72 hours			
	Imatinib	31% (19)	Human neonatal blood	400 mg/body	16 hours	12% (12/100)	0% (0/6)	2% (2/101)

[a]Small for gestational age was identified as body weights that were <10th percentile of the normal population based on sex and gestational age at birth or as reported by the authors when clearly defined.
[b]Unpublished data.

likelihood of low birth weight (27). Additionally, reports have indicated that the rate of stillbirths is also increasing (27).

Moreover, there are also cases in which bone marrow suppression, thought to be caused by chemotherapy, is observed during the perinatal period. However, this spontaneously improves after a few weeks (8).

Anthracycline antibiotics

Epirubicin and doxorubicin have demonstrated a low rate of placental transfer at approximately 1–10% during animal experiments (9,11). However, idarubicin is highly liposoluble and has a long half-life. Therefore, this drug may demonstrate a high rate of placental transfer.

Doxorubicin is the most frequently used anthracycline antibiotic. There is one reported instance in which a few subjects in a prospective study of breast cancer received 5-FU, doxorubicin and cyclophosphamide (FAC) therapy from the second trimester onwards. There were no reported increases in short-term adverse events (e.g. congenital anomalies) and thus it was believed that it could be administered relatively safely (4,28). However, a relationship has been suggested between serious effects on the fetus, fetal mortality rate, daunorubicin and idarubicin. The administration of cytarabine and doxorubicin from the second trimester onwards has been proposed for treating acute myeloid leukemia during pregnancy (29).

In addition, anthracyclines exhibit dose-dependent cardiotoxicity. No consensus has yet been reached regarding cardiotoxicity in fetuses due to anthracyclines administered during pregnancy.

While there are some reports indicating that no decrease in cardiac function was observed with either epirubicin or doxorubicin, there are also studies indicating that cardiac function disorders were observed after idarubicin administration (30–32). Therefore, drug selection for pregnant cancer patients remains controversial.

Taxanes

The placental transfer of taxanes, which are important for the chemotherapeutic management of breast cancer and gynecological cancer, is reported to be low at 1–2%. However, despite the low concentrations, long-term exposure could occur as the drug may remain in the fetal tissues (10). The results of animal experiments indicate that the drugs were detected in the fetal tissues even 72 hours after taxanes had been administered to the dams, which was thought to be due to the high liposolubility and tissue affinity of taxanes (10). Docetaxel has a higher tissue affinity than paclitaxel. In addition, CYP3A4, one of the enzymes that metabolize taxanes, is not expressed in fetal livers (33,34). For this reason, embryotoxicity and fetotoxicity are enhanced, suggesting an increased likelihood of intrauterine fetal death (IUFD) and decreased body weight. However, no increase in fetal or maternal complications was reported despite the use of taxanes during pregnancy, when compared with conventional chemotherapy during a cohort study conducted in clinical practice (35).

Compared with anthracyclines, there is less data available for taxanes. Therefore, when clinical treatment of breast cancer is required, weekly paclitaxel has been approved for use from the second trimester onward (4). Furthermore, in the field of obstetrics and gynecology, when used together with platinum-based drugs, some consider taxanes as the first choice, even when treating pregnant patients (3,36).

Alkylating agents

Placental transfer of cyclophosphamide has been observed and, when administered 1 hour before a cesarean section, it can be detected in the amniotic fluid at a concentration of approximately 25% (37). An increased rate of congenital skeletal malformations was observed when cyclophosphamide was administered during the first trimester, similar to that for the treatment of autoimmune diseases (38–40). However, there are several reports of its use in combination with anthracyclines, and it can be administered relatively safely from the second trimester onwards (41,42).

There is extremely limited available data regarding the placental transfer and rate of congenital malformations when using dacarbazine, which is used to treat Hodgkin's lymphoma and malignant melanoma. Therefore, caution is required, as there are some reports of major malformations and IUGR associated with this form of treatment (43,44).

Antimetabolites

5-FU formulations are used to treat all types of cancer as a monotherapy, or as part of polypharmacy regimens. Rejimens of FAC and FEC (5-FU, epirubicin and cyclophosphamide) are recommended when selecting anticancer drugs for pregnant breast cancer patients and are permitted for use as required (3,4). However, if used during the first trimester, the rate of spontaneous miscarriage increases, in addition to the issue of teratogenicity. Furthermore, caution must be exercised even if administered from the second trimester onwards, as there have been reports of IUGR and IUFD (45,46).

Methotrexate is also indicated for hematological and breast cancer treatment and its oral version is widely used as an anti-rheumatoid arthritis drug. When patients with rheumatoid arthritis wish to bear a child, a drug cessation period of 3 months is recommended before conception. Injectable formulations of methotrexate are used to induce the miscarriage of extrauterine pregnancies, but oral formulations are contraindicated during pregnancy. In addition, the administration of doses of more than 10 mg/week prior to pregnancy may cause aminopterin syndrome, which involves a variety of fetal morphological abnormalities (27). Since there is often an alternative drug for any cancer, its use should be avoided unless absolutely necessary (41).

Cytarabine is used to treat acute myeloid leukemia and is a very important drug. However, it has been reported to cause major malformations, IUGR and stillbirth when administered during pregnancy (27,47). Accordingly, murine experiments have shown that the rate of placental transfer is relatively high at 56.7%, and thus cytarabine may cause a higher rate of stillbirth than other anticancer drugs (11). However, there are also reports stating that acute myeloid leukemia increases the rate of stillbirth and there is still room for discussion regarding the relationship between the rate of adverse effects with cytarabine (48,49).

Vinca alkaloids

Vinca alkaloid formulations have a relatively high plasma protein-binding rate, suggesting that they may have relatively small effects on the fetus (5,50). However, there have been several reports of major malformations when it is used in combination with other drugs and even as monotherapy; therefore, caution is required (51). Additionally, the placental transfer rate of vinblastine was found to be 15% during animal experiments on baboons (9).

Vincristine and vinblastine are used to treat malignant lymphoma. Hodgkin's lymphoma treatment includes vinblastine as part of the ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) regimen and non-Hodgkin's lymphoma therapy includes vincristine as a part of the CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) regimen. These treatments have also been shown to be effective, even during pregnancy (29). Although there have been reports of adverse fetal events, use of these regimens is recommended from the second trimester onwards (3).

Platinum agents

The placental transfer of carboplatin was found to be high at 57.5% during experiments using baboons (10). Moreover, experiments using mice demonstrated that plasma concentrations above those found in the females were observed in the fetuses (11). In addition, human studies of cisplatin revealed that concentrations of between 31% and 65%, found in the maternal blood, were also measured in the umbilical cord blood (13). Therefore, platinum-based formulations are assumed to have an extremely high rate of placental transfer. However, compared with other drugs, there are no reports of obvious increase of congenital malformations or major effects of platinum-based formulations on the fetus. Therefore, the administration of carboplatin is recommended for non-small cell lung cancer or ovarian cancer from the second trimester onwards as well as the administration of cisplatin for germ cell tumors (3).

Hormonal agents

Tamoxifen

Tamoxifen is used in patients with breast cancer which demonstrates sensitivity toward premenopausal hormones. However,

regarding the effects of tamoxifen during pregnancy, the available case reports involve recurrent breast cancer, and no obvious tumor-shrinking effects were observed due to tamoxifen. Furthermore, progression of the disease during late pregnancy, when estrogen levels increase, was noted (52).

In addition, regarding safety, since a relationship with congenital abnormalities (including Goldenhar syndrome, ambiguous genitalia and Pierre Robin syndrome) has been suggested, tamoxifen should never be used at any stage during pregnancy (41). If hormone therapy is required, it should be administered during the postpartum period.

Molecular targeted agents

Most monoclonal antibodies (mAbs) have large molecular weights and are hydrophilic. Similar to maternal Immunoglobulins G, the placental transfer of mAbs actively occurs via a specific receptor-mediated mechanism from gestational Week 16 onwards. Therefore, they are believed not to cause any major fetal malformations in the first trimester (53,54). On the other hand, tyrosine kinase inhibitors (TKIs) are low-molecular weight compounds known to cross the placenta during the first trimester and have been suggested to cause several disorders, such as increases in the rate of spontaneous miscarriage.

Human epidermal growth factor receptor Type 2 inhibitors

The human epidermal growth factor receptor Type 2 (HER2) pathway plays an important role in the normal development of the heart and nervous system during fetal organogenesis and may also be involved during conception and implantation (55,56). Trastuzumab is an important drug for the treatment of HER2-positive breast cancer overexpressing HER2. It is also used to treat advanced HER2-positive gastric cancer.

Compared with non-pregnant patients, one of the pathological characteristics of breast cancer diagnosed during pregnancy is that many cases are found to be hormone receptor-negative (57). Although there are also reports that the tumors are more often HER2-positive, this remains controversial (57).

Trastuzumab administration from the second trimester onwards is known to increase the risk of oligohydramnios (58). The main hypothesis for this suggests that because HER2 is expressed in the fetal kidneys, trastuzumab administration affects fetal urine production and amniotic fluid reabsorption (59,60). In addition, the expression of vascular endothelial growth factor (VEGF), which regulates the production and reabsorption of amniotic fluid by altering the permeability of the fetal membranes, is also believed to be inhibited by trastuzumab (61,62). The oligohydramnios that occurs due to these mechanisms increases the risk of premature delivery and, as a result, neonates often present with respiratory and renal failure. Sarno et al. (53) reported that cases receiving trastuzumab during pregnancy demonstrated a neonatal mortality rate of 21%, due to multiorgan failure caused by oligohydramnios. However, oligohydramnios caused by trastuzumab improves when the drug is discontinued, thereby indicating reversibility (58).

Some studies, however, have found that no neonates were born with congenital malformations when trastuzumab was inadvertently administered in cases of unexpected pregnancy during postoperative adjuvant chemotherapy for breast cancer (63). This may be because it is difficult for trastuzumab to actively reach the fetus via the placenta during the first trimester. However, data regarding trastuzumab use during pregnancy are limited; an observational study targeting pregnant HER2-positive breast cancer patients who received anti-HER2 drugs (NCT00833963) is underway and the results are eagerly anticipated. However, considering the current data and guidelines, trastuzumab should not be administered during pregnancy.

Other molecular targeted drugs against HER2 include pertuzumab, T-DM1 and the TKI lapatinib. Despite the promise of these therapies, there is currently no data to verify the safety of any of these drugs. Pertuzumab is used in combination with trastuzumab and T-DM1 is an antibody-drug conjugate that consists of trastuzumab linked to the cytotoxic agent emtansine. Like trastuzumab, these drugs should not be administered during pregnancy. Lapatinib, a low-molecular weight compound, is believed to cross the blood–placenta barrier, beginning in the first trimester. Results from reports of cases exposed to lapatinib in the first trimester indicate that healthy infants were delivered (64). However, since the safety of lapatinib is unknown, similar to TKIs in general, it should not be administered during pregnancy.

Epidermal growth factor receptor inhibitors

The epidermal growth factor receptor (EGFR) pathway is not only associated with cell proliferation and differentiation but is also involved in various stages of embryonic development. Experiments using mice have shown that an inhibited EGFR pathway leads to impaired maturation of the skin, lungs and gastrointestinal tract epithelium, resulting in increased fetal death (65,66). Similar to the HER2 pathway, it is also implicated in conception and implantation, as well as fetal renal maturation and the migration and differentiation of cerebral cortical cells (67–69).

Gefitinib and erlotinib, the low-molecular weight EGFR-TKIs, are important drugs for treating lung cancer patients with EGFR gene mutations. In animal experiments, when erlotinib was administered during organogenesis and the plasma concentration was comparable to that in humans, no increase in fetal death or miscarriage rates were reported. However, when the concentration was increased by 3-fold, there was an increase in fetal death and miscarriage. In addition, the rate of miscarriage increases when erlotinib is administered from the first gestational week (70).

To date, there have been only approximately 60 reported cases of lung cancer diagnoses during pregnancy (71). Among these, there are five reports in which EGFR-TKIs were used; in all cases, delivery occurred without evidence of congenital malformations (17,18,70,72,73). However, two cases of IUGR due to oligohydramnios were observed, and a reversible increase in hepatic enzymes was observed in one other case (twin pregnancy) (18,73). Gefitinib and erlotinib crossed the placenta and reached the fetus; with reports evaluating their pharmacodynamics indicating that approximately 20% of the maternal plasma concentration of gefitinib was observed in the cord blood (17). Similarly, approximately 25% of the maternal concentration of erlotinib was observed in cord blood (18). According to international guidelines, carboplatin and paclitaxel can be used for the chemotherapeutic management of lung cancer, from the second trimester onwards (3). Moreover, as reports regarding EGFR-TKIs are also limited, these drugs should not be administered to pregnant lung cancer patients. However, if the lung cancer prognosis is very poor, it is worth further investigation, depending on the situation—since the effect of gefitinib or erlotinib on the fetus may be pharmacokinetically limited.

There is no clinical data regarding the use of the anti-EGFR antibody drugs, such as cetuximab and panitumumab, during

pregnancy. However, we presume that they are pharmacokinetically similar to other mAbs.

Angiogenesis inhibitors

The signal transduction pathways that involve VEGF play an important role in placental angiogenesis and neovascularization, as well as embryogenesis and normal fetal maturation (74,75). VEGF also plays an important role in the permeability of fetal membranes, regulating the volume of amniotic fluid and embryonic implantation, with a suggested relationship to infertility (76). During animal experiments, the inhibition of the VEGF pathways causes hypertension, proteinuria, glomerular endotheliosis and preeclampsia. This has a negative impact on normal placenta formation and increases the risk of IUGR (77,78).

Bevacizumab, the VEGF antibody-based drug, is used to treat an extensive range of cancer types. Moreover, tumor shrinkage and improvement in survival time have been noted when this drug is used in combination with chemotherapy. Experiments using rats have demonstrated that fetal death, low body weight and skeletal abnormalities are observed at the equivalent concentrations as used in humans (79). There are no reports of intravenous administration of bevacizumab during pregnancy. However, there are its post-marketing surveillance reports that state it has been administered to pregnant women and that malformations were observed, although the exact details are unknown (14). In contrast, intravitreous administration of bevacizumab has been used to treat choroidal angiogenesis and diabetic retinopathy in the field of ophthalmology. Although there are cases in which it has been administered safely (80,81), studies involving primate models have shown that the drug reaches systemic circulation even when it is administered to the vitreous humor (82). In these studies, there were also cases of spontaneous miscarriage when the drug was administered during the first trimester and therefore caution is required when performing intravitreous administration (83).

Sunitinib is a low-molecular weight multikinase inhibitor used to treat renal cell carcinoma and gastrointestinal stromal tumors (GIST). This drug caused fetal and embryonic developmental disorders resulting in fetal death during animal experiments when administered at doses commonly used in humans (84). However, there are no such reports in humans.

Thus, inhibitors of angiogenesis should not be administered, as it is highly likely that they will affect the fetus from embryonic implantation until late gestation.

Rituximab

Rituximab is an antibody-based drug against the CD20 antigen, and it dramatically improves the prognosis of malignant B-cell lymphoma.

Rituximab is known to be actively transferred to the fetus from the second trimester onwards. When comparing rituximab concentrations in mothers and neonates at the time of delivery, the concentrations measured in the neonates were approximately 1.5–3-fold those measured in the mothers, even 2–3 months after the final administration, demonstrating that the drug remains present in the fetal blood for a long period (15,16). Due to these effects, lymphopenia and B-cell depletion are observed in many of the neonates born to patients who received rituximab during pregnancy. However, this effect is reversible, with neonates recovering within a few months, although there are reports stating that no increased risk of pregnancy-related complications and morphological abnormalities were observed (85,86).

Thus, rituximab may be administered during pregnancy if required. Although the effects of rituximab on the fetus in the first trimester are considered to be low, a study of the relationship between pregnancy and rituximab administration reported a spontaneous abortion rate of 21% (15). The drug may cause a latent increase in the risk of miscarriage. In addition, the fact that neonatal hematopenia increases the risk of infection must also be considered.

Imatinib

Imatinib, the low-molecular weight compound, is a drug that plays an important role in the treatment of chronic myeloid leukemia (CML) expressing the 'BCR-ABL' fusion gene. It is also used to treat KIT-positive GIST and Philadelphia chromosome-positive acute lymphocytic leukemia.

In animal experiments, administration of doses that were approximately equivalent to the clinical doses for humans in the early stages of a pregnancy affected early embryogenesis by causing an increased rate of post-implantation mortality and decreased fetal body weight (87). Furthermore, teratogenicity was observed with cranial defects, such as exencephaly and encephaloceles. The most commonly reported morphological abnormalities were defects of the skeletal system (87). It is hypothesized that the morphological abnormalities may be caused by the fact that platelet-derived growth factor receptor α, which plays an important role in organogenesis, is inhibited by imatinib (88).

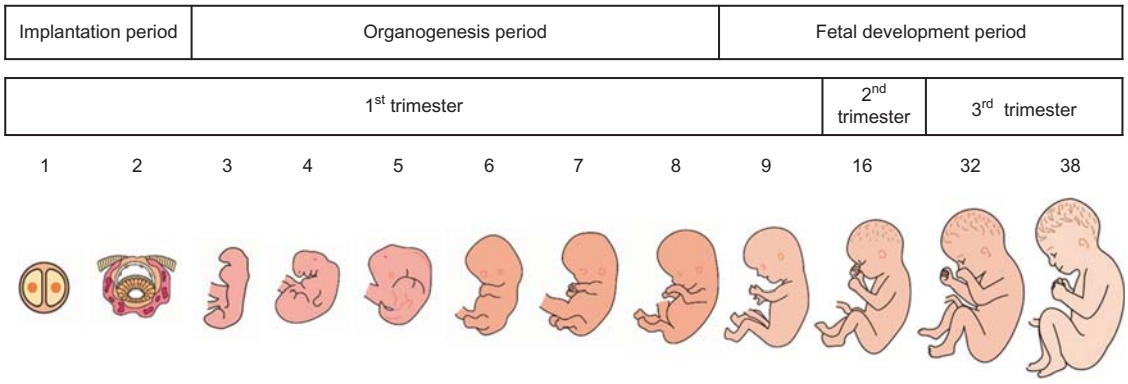
Imatinib has been shown to undergo placental transfer to the fetus and Ali et al. (19) reported detecting the drug at a concentration approximately 30% that of the maternal concentration in neonatal peripheral blood. In addition, when imatinib was administered during the first trimester, the rate of spontaneous abortion was relatively high at 17% (8). Major malformations also occurred in 12% of cases. A report by Pye et al. stated that among the 12 cases in which major malformations were observed, the majority had skeletal system abnormalities. A total of eight children were delivered, one was stillborn and three pregnancies underwent an artificial termination (89). Based on the above findings, imatinib should not be administered during pregnancy.

Pregnancy during chemotherapy

When patients receive chemotherapy, contraception should be actively encouraged throughout the treatment period (3). Additionally, contraception for the first 3–6 months following the final administration of chemotherapy is recommended (3). If the patient is pregnant while receiving chemotherapy, termination of pregnancy is an option as there is an increased risk of drug-induced fetal malformations.

Patients with breast cancer sensitive to premenopausal hormones may miss their opportunity to become pregnant, as the postoperative administration of tamoxifen may be long term (90). However, if therapy is discontinued early, the risk of recurrence increases, and therefore the patients wishing to bear a child and their clinicians may be faced with a dilemma. At present, the timing of tamoxifen discontinuation is determined on an individual case basis, once discussed sufficiently with the patient. Meanwhile, the ongoing POSITIVE trial (NCT02308085) examines the effects of tamoxifen discontinuation for a maximum of 2 years on the occurrence of pregnancy.

It is difficult for mAbs to pass through the placenta during the early stages of pregnancy. Moreover, when mAbs are discontinued, continuing with the pregnancy is an option (54). TKIs, on the other hand, cross the placenta from the first trimester onwards; imatinib



Cytotoxic agents	Extremely high risk	Observed in 20%	Relatively high rate of complications in the mother and fetus (e.g., IUGR)
Monoclonal antibodies	Moderately high risk	Relatively low	High rate of drug-specific complications (e.g., oligohydramnios and lymphopenia)
Tyrosine kinase inhibitors	Moderately high risk	Potential	Complications may occur in the mother and fetus (insufficient data)

Death of embryo and spontaneous abortion common	Major malformation	Functional defects Minor malformation

Figure 1. Administration risks for each anticancer drug during the stages of pregnancy and their effects on the fetus.

in particular has been shown to increase the rate of fetal morphological abnormalities and abortion. Therefore, patients may miss the opportunity to fall pregnant during these treatments. However, when adult patients with CML have experienced complete molecular remission for 2 years or more, 40% of those cases were able to temporarily discontinue imatinib administration. Moreover, by readministering imatinib to treat cases of recurrence, complete molecular remission was demonstrated in all cases (91). In addition, since there have been no reports of major malformations when used from the second trimester onwards, it may be of value to investigate whether it is possible to become pregnant by discontinuing or readministering the drug, even when patients are treated with imatinib. However, there is currently no data available on other TKIs and thus we believe that continuing pregnancy would be at risk.

Discussion

Since the publication of a case report on the use of urethane during chemotherapy to treat a pregnant CML patient, perspectives regarding the administration of anticancer drugs during pregnancy have gradually been established (Fig. 1) (92). Additionally, the threshold for treating pregnant cancer patients with chemotherapy has become low. However, there are several points that remain to be elucidated.

For example, with regard to the doses of the anticancer drugs, there is no evidence-based data regarding whether to calculate the dose based on the current body weight and body surface area during pregnancy or whether to use pre-pregnancy values. According to international recommendations, performing administration based on the actual body weight is recommended (41).

In addition, the plasma volume and cardiac output in pregnant women continue to increase until the end of the second trimester, resulting in physiological changes such as increased glomerular filtration rate and creatinine clearance (93,94). We presume that these changes cause decreased plasma concentrations of anticancer drugs. In studies of the pharmacokinetics of some small-scale anticancer drugs when treating pregnant cancer patients, the area under the curve (AUC) and peak plasma concentration both decreased while clearance increased (95,96). For paclitaxel in particular a 27.4% decrease was noted in the AUC. Therefore, we estimate that a dose increase of 37.8% is required to achieve an AUC equivalent to that of non-pregnant women (96). Cohort studies have reported no differences in the treatment outcomes of pregnant breast cancer patients compared with non-pregnant patients (97). However, chemotherapy in clinical practice may be administered at lower doses. The optimal dose for the administration of anticancer drugs that will achieve maximal effects in the mother must be determined, taking pharmacokinetics into consideration. However, this is extremely difficult due to its complexity and individual variation. At the very least, pregnancy should not be the reason for decreasing the dose of anticancer drugs.

Amant et al. (25) conducted a prospective multicenter study regarding the effects on children whose mothers received cancer treatment during pregnancy. They found that the cognitive development and physical health outcomes at 1.5 and 3 years of age were equivalent to those of children born to mothers who did not have cancer. Furthermore, no increase in the rate of reduced cardiac function was reported, although the observation period was short. This does not necessarily apply to all types of cancer and therapeutics, but supports the fact that a diagnosis of cancer during pregnancy should not necessarily be a reason for termination due to potential effects on the fetus.

However, there have been recent developments in drug treatments, such as the novel molecular targeted drugs and immune checkpoint inhibitors. The knowledge gained to date using cytotoxic anticancer drugs often does not apply when these newer drugs are administered to pregnant women. Decisions can be made based on

the characteristics of mAbs and TKIs; however, there are still many unclear points. Therefore, treating pregnant cancer patients with these types of drugs remains a largely unknown territory.

Summary and conclusions

The number of patients diagnosed with cancer during pregnancy is expected to continue to increase. In practice, patients and their families must make the extremely difficult decision of whether to continue or terminate the pregnancy in a limited period of time. The clinician should explain that termination is not the turning point that necessarily results in clinical improvement of the cancer. The treatment options must be suggested in the context of the limited evidence that is available. Indeed, this process is associated with increased psychological stress for all parties. In addition, the most important aspect is that there are many challenges associated with cancer during pregnancy, including those that may occur in the mother or child postpartum. Another important aspect concerns those patients who desire to bear children during treatment with oral tamoxifen or imatinib. These difficult problems must be approached by a team of specialists, including obstetricians, oncologists, hematologists, as well as psychiatrists, psychologists and other paramedical professionals. We believe that a multidisciplinary approach will allow all medical professionals to offer patients the highest quality of care.

Conflict of interest statement

None declared.

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