

Cancer Treatment during Pregnancy

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Introduction

The diagnosis of cancer during pregnancy is relatively uncommon. However, with the rising trend of delaying childbearing, more cancer patients are expected to be diagnosed during the course of gestation. The exact incidence is unknown, although it is estimated that around 1 in 1000 pregnancies is complicated with cancer. Pregnant patients are often diagnosed with cancer at relatively late clinical stages, which makes delaying therapy until delivery not feasible in the majority of cases. Induction of abortion could be proposed, even if there is no evidence supporting a therapeutic role for this approach. In addition, it is considered ethically unacceptable by some individuals and cultural groups. In this chapter, we will provide key tips on managing pregnant cancer patients and discuss in greater detail the most common tumours diagnosed during pregnancy.

Diagnostic Radiology and Radiation Therapy

Radiation doses greater than 100 mGy may result in up to 1% risk of childhood cancer and foetal malformations. However, staging procedures that involve radiation exposure are usually below this dose. Nevertheless, it is preferred to strictly limit their use during pregnancy. Chest x-ray could be performed to rule out pleural or lung pathology, yet with adequate

abdominal shielding. Abdominal ultrasound is quite safe and can be used to evaluate the liver and abdominal organs. Computed tomography, bone and fluorodeoxyglucose–positron emission tomography (FDG-PET) scans should be strictly avoided during pregnancy. Magnetic resonance imaging (MRI) without gadolinium could serve as a better alternative in the event that an abdominal ultrasound or chest x-ray shows suspicious or inconclusive findings. Whole-body MRI may be an interesting approach for pregnant cancer patients, as it provides a fast and accurate evaluation of the whole body without exposure to radiation or contrast material. However, experience with this technique is rather limited to only a few centres worldwide.

Radiation therapy is better postponed following delivery. Patients with brain metastasis often require immediate palliative radiotherapy, and this can be performed during pregnancy, provided adequate shielding is established. Palliative radiotherapy to the cervical spine, upper thoracic vertebrae and shoulders is also possible as the radiation fields are rather far from the uterus. Radiation to the pelvis and lumbar area should be avoided during the course of gestation. In case there is an urgent need for such treatment, abortion should be considered.

Systemic Anti-cancer Therapies

Chemotherapy during Pregnancy

The administration of chemotherapy during the first trimester is associated with a considerably higher rate of spontaneous abortion and congenital malformations. Hence, chemotherapy should be avoided during this period, if at all possible. In cases in which it is urgent to start chemotherapy for maternal advanced disease during the first trimester, abortion should be considered.

Generally, exposure to chemotherapy following the first trimester does not appear to be associated with major foetal complications, particularly in the short term. However, preterm labour and pregnancy-related complications (e.g. gestational diabetes, premature rupture of membranes) appear to be higher in cancer patients treated with chemotherapy compared to those exposed only to surgery. Thus, administering standard therapy

during pregnancy might not be feasible in all cases, and in some situations customised strategies could be adopted. Among such strategies, weekly fractionation of the chemotherapy dose emerges as an attractive approach. It is associated with a lower peak plasma concentration of the drug, which lowers the chances of placental crossing. In addition, it allows close monitoring of the pregnancy and easy interruption of the drug administration, if needed.

Importantly, the safety of the different chemotherapeutic agents is not equivalent when administered during pregnancy (Table 1). Some agents should be avoided even during the second and third trimester. This will be covered in more detail in the subsequent sections.

The pharmacokinetics of most chemotherapeutic agents is altered during pregnancy. These drugs are partly metabolised by the placenta, resulting in a reduced maximum plasma concentration (C_{\max}) and a higher renal clearance when administered during pregnancy. However, it is not clear whether this has any clinical implications on their efficacy during pregnancy. Using higher dosages of chemotherapy during pregnancy is not recommended, but the actual body weight should be used, without adapting for the pregnant state.

Table 1 *Estimated Risk of Pregnancy Complications with Systemic Anti-cancer Therapy When Administered during the Second and Third Trimester of Gestation*

High risk: "prohibited"	Medium risk: "use with caution"	Low risk: "allowed"
Idarubicin	Cisplatin	Vinblastine
Daunorubicin	Carboplatin	Vincristine
Methotrexate	Cyclophosphamide	Doxorubicin
Trastuzumab	Rituximab	Epirubicin
Bevacizumab	Imatinib	Paclitaxel
Tamoxifen	All-trans-retinoic acid (ATRA)	Docetaxel
Zoledronic acid	Ifosfamide	Interferon-alpha

Note: This classification is not based on the Food and Drug Administration classification, but rather on the interpretation made by the authors of the limited available preclinical and clinical data.

Hormonal Agents during Pregnancy

The use of tamoxifen during pregnancy has been shown to be associated with ambiguous genitalia in animals. Similar observations were also noted in sporadic case reports in humans. Thus tamoxifen should be avoided during pregnancy. Caution is advised in young breast cancer patients who are on tamoxifen as a part of their adjuvant therapy. These patients should be asked to use contraception during treatment. If pregnancy has occurred, patients should be informed that there is a potential risk of foetal malformations secondary to tamoxifen in order to make an informed decision on whether they would like to proceed with the pregnancy.

Monoclonal Antibodies during Pregnancy

Monoclonal antibodies are large molecules that require active transport to cross the placenta and reach the foetus. Such mechanism is activated only following the first trimester. Hence, unlike chemotherapy and hormonal agents, early exposure to monoclonal antibodies is unlikely to be associated with foetal defects. This could be relevant in patients who become accidentally pregnant during maintenance therapy (trastuzumab in breast cancer; rituximab in non-Hodgkin's lymphoma). In these cases, the drug should be stopped once pregnancy has been established, yet abortion does not need to be considered. In pregnant cancer patients, prolonged administration of monoclonal antibodies following the first trimester could be associated with major pregnancy and foetal complications. This is rather drug-dependent and will be discussed in more detail in the subsequent sections.

Supportive Care

Nausea and vomiting

Active or proactive treatment with metoclopramide, domperidone or ondansetron is possible throughout the pregnancy period. Prednisone could also be used, but preferably during the second trimester.

Pain

Paracetamol is the analgesic of choice. Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, as they are associated with foetal

defects, risk of miscarriage and oligohydramnios. Opiates could be used in cases of severe pain, but they are better avoided close to delivery, as they can be associated with neonatal withdrawal effects.

Infections

Cephalosporins, metronidazole and clarithromycin could be used safely during pregnancy. Limited data are available on imipenem and meropenem. Quinolones and aminoglycosides should be avoided during the course of gestation, as they are associated with foetal congenital malformations.

Anaemia and leukopenia

Erythropoietin and granulocyte-colony stimulating factor (G-CSF) should not be used unless there is an urgent need for them, given the limited safety data on their use during pregnancy.

Osteoporosis and bone metastases

Bisphosphonates were shown to induce foetal skeletal defects in animal models. They can also cause maternal hypocalcaemia, which could affect uterine contractions and hence should be avoided.

Obstetrical Care and Pregnancy Monitoring

Whenever possible, pregnant patients with cancer should be treated within institutions with known expertise in managing such cases and within a multidisciplinary team including an oncologist, obstetrician, neonatologist and also a psychologist. These pregnancies should be considered at high obstetrical risk, and hence should be closely monitored. Monthly ultrasounds should be performed to monitor foetal growth, particularly in patients receiving chemotherapy or those with advanced disease. Prophylaxis of deep vein thrombosis with low molecular weight heparin could be considered, particularly in obese patients and in those older than 35 years of age, given the hypercoagulable state of pregnancy as well as the prothrombotic effect of cancer.

Every effort should be made to complete the pregnancy to term. Preterm delivery has been associated with short- and long-term adverse effects

on the newborn. In addition, it has no positive implications on maternal prognosis. In cases in which waiting until full term is not possible, later preterm delivery (i.e. starting week 35) could be an alternative.

Delivery should be avoided during nadir periods in patients receiving systemic chemotherapy. In patients treated with 3-weekly regimens, chemotherapy should be avoided after the 34th week of gestation, as these regimens have relatively long nadir periods. Weekly regimens have shorter nadir periods and hence could be administered closer to term, if needed. Regardless of the chosen regimen, blood counts, liver and kidney functions tests should be performed prior to each chemotherapy administration.

In patients who need chemotherapy shortly after giving birth, vaginal delivery should be preferred to caesarean section, as recovery following vaginal delivery is typically faster. Vital signs, weight, height, head circumference and Apgar score of all neonates should be checked. Long-term foetal follow-up is highly recommended and this would be better performed through any of the currently available registry programs (www.cancerinpregnancy.org or www.pregnantwithcancer.org).

Common Cancers during Pregnancy

Breast Cancer

Breast cancer is the most commonly diagnosed cancer during pregnancy. Once a patient is diagnosed, she should be approached in a similar way as young breast cancer patients, taking into consideration the gestational age at diagnosis. Patients with small locally-confined tumours should be considered for primary surgery. In general, surgery could be performed any time during pregnancy, but a careful monitoring of maternal and foetal conditions is advised, particularly after the 25th week of gestation. The choice of surgery is the same as in the non-pregnant setting. Patients subjected to conservative breast surgery should receive adjuvant radiation therapy, which in general should be postponed until after delivery. In patients requiring surgery early during the first trimester, the expected delay in receiving radiotherapy could favour performing mastectomy in some of these cases, particularly those who are at a high risk of devel-

oping local recurrence. No foetal defects secondary to sentinel lymph node biopsy (SLNB) have been observed, acknowledging the limited published data in this regard. Hence, it could be considered in centres in which SLNB is routine practice in the non-pregnant setting.

Chemotherapy should be considered in patients with (1) metastatic disease at presentation, (2) large tumours requiring neoadjuvant therapy and (3) adverse prognostic features at surgery necessitating adjuvant therapy. Anthracycline-based regimens remain the chemotherapy of choice during pregnancy. Both epirubicin and doxorubicin can be safely administered. As for taxanes, transplacental transfer is very low and emerging clinical data are rather reassuring regarding their safety. Weekly paclitaxel does not require high-dose steroid preparation and is less toxic compared to 3-weekly docetaxel, and hence is preferred in pregnant breast cancer patients. On the other hand, regimens such as cyclophosphamide, methotrexate and fluorouracil (5-FU) (CMF) should be completely avoided, given the high abortive properties of methotrexate and the lack of particular importance of such a regimen in current breast cancer management.

Patients with HER2-positive breast cancer are candidates for treatment with anti-HER2 targeted agents. Trastuzumab increases the risk of developing oligohydramnios, a condition that can lead to premature delivery, foetal morbidity and mortality. This is believed to be secondary to the effect of trastuzumab on the foetal kidney, which expresses HER2 and is responsible for the amniotic fluid production. Currently, we lack any data on the safety of other HER2-targeted agents. Hence, all anti-HER2 targeted agents should be avoided during pregnancy.

Occasionally, pregnant breast cancer patients are diagnosed with small (e.g. pT1), node-negative, low-grade endocrine-sensitive tumours (i.e. luminal-A breast cancer). Outside pregnancy, chemotherapy is often not offered to these patients. Given that hormonal agents are contraindicated during pregnancy, these patients could be offered only surgery during pregnancy, postponing hormonal therapy along with radiation therapy, if indicated, following delivery.

Haematological Tumours

Pregnant patients diagnosed with acute leukaemias or aggressive lymphomas often require the prompt initiation of chemotherapy. Hence, in the majority of cases diagnosed during the first few weeks of pregnancy, abortion should be considered, as a delay in the initiation of therapy could significantly hamper the patient's prognosis.

In lymphomas, the standard ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) and CHOP (cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone) regimens can be safely administered following the first trimester in patients with Hodgkin's and non-Hodgkin's lymphoma, respectively, with no obvious increase in foetal or pregnancy-related complications. The use of rituximab in patients with B-cell lymphomas has been shown to be associated with foetal B-cell depletion at delivery, which is generally reversible. Hence, in patients in whom the use of rituximab during pregnancy is deemed necessary, the drug could be administered, acknowledging that this might have a transient effect on foetal immunity at delivery.

Managing acute leukaemias during pregnancy is very challenging. The use of anthracycline analogues, such as daunorubicin and idarubicin, is preferably avoided during pregnancy, even following the first trimester. They are highly lipophilic, resulting in high placental crossing and serious foetal complications irrespective of the timing of exposure. An alternative could be doxorubicin, which is safer during pregnancy and has considerable activity in acute leukaemia as well. Patients with promyelocytic leukaemia require treatment with all-trans-retinoic acid as well, which can be safely administered starting from the second trimester.

The use of imatinib in patients with chronic myeloid leukaemia has been shown to be safe following the first trimester. When treatment is required during the first trimester, interferon could be used as an alternative, as it is a large molecule and does not cross the placenta. In addition, clinical data clearly support its safety when administered during the first trimester.

Gynaecological Tumours

Cervical cancer is the second most common tumour diagnosed during pregnancy. Radiation therapy is the standard of care in early stages but this would compromise the continuation of pregnancy and hence should be avoided. Otherwise, abortion should be considered. Lymphadenectomy should be considered in patients with positive lymph nodes and neoadjuvant chemotherapy with a cisplatin-based regimen could be considered until delivery.

Patients with epithelial ovarian cancer are often diagnosed at an advanced stage and require systemic chemotherapy. The combination of weekly paclitaxel and carboplatin is the preferred option until delivery. Radical surgery could be considered at the time of delivery. No clinical data are available on the safety of bevacizumab during pregnancy. However, preclinical data have shown developmental anomalies and interference with embryonic development. Hence, bevacizumab presently should not be used during pregnancy.

The use of standard BEP (bleomycin, etoposide and cisplatin) or EP (etoposide and cisplatin) regimens during gestation seems feasible, although the use of etoposide during pregnancy has been shown to be associated with relatively high risk of pregnancy and foetal complications. An alternative could be paclitaxel and cisplatin. No apparent increases in foetal toxicities have been reported using these regimens.

Declaration of Interest:

Dr Azim Jr has reported no conflicts of interest.

Dr Peccatori has reported no conflicts of interest.

Further Reading

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