Chemotherapy During Pregnancy for Advanced Colon Cancer: A Case Report

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Clinical Practice Points

- Chemotherapy for colorectal cancer during pregnancy has been reported in a few cases, mostly with 5-fluorouracil and oxaliplatin, in the later stages of pregnancy.
- We report a case of a pregnant woman diagnosed with metastatic colon cancer who received FOLFOX during pregnancy from the end of the second trimester.
- Chemotherapy was effective and tolerable for the patient and child. Fetal growth was monitored closely and delivery planned.
- MRI was used for diagnostics and response evaluation.
- Multidisciplinary collaboration regarding staging, treatment, follow-up and care is necessary for these patients.
- There are a few literature reviews summarizing the available evidence that provide guidance in these uncommon clinical scenarios.
- This case report presents our experience of chemotherapy in this challenging situation.

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Introduction

Colorectal cancer (CRC) is a common cancer worldwide. An increasing incidence in young adults has been reported in recent years,[1,2] and specifically in Europe.[3,4] Although some cases are related to inherited susceptibility, most are sporadic cancers. Early-onset CRC are more often left sided, present at a more advanced stage, and with more aggressive histologies.[5,6] The incidence of malignancy and pregnancy is estimated at 1:1000 pregnancies, with an estimated incidence of CRC of 1:13,000.[7] With increased cancer incidence and delayed child-bearing, the occurrence of CRC during pregnancy is expected to increase.[8] Although rare, CRC in young adults has large impact on life and multiple aspects of quality of life.[9] A diagnosis of CRC during pregnancy imposes therapeutic challenges in addition to major psychosocial issues. Consideration must be given to the patient in need of effective cancer treatment, the fetus' growth and development, and to palliation and patient care in cases of noncurative treatment intent.

Systemic chemotherapy is the treatment of choice for patients with advanced CRC. It is in general questionable to use chemotherapy during pregnancy because of the risk of harming the fetus. For CRC, there are some case reports,[10-17] patient series,[18] and literature reviews[8,19,20] of chemotherapy during pregnancy; most have reported on treatment with 5-fluorouracil (5-FU) and oxaliplatin (FOLFOX).[8,10-15,17,18] Case reports of patients treated with FOLFOX during pregnancy for metastatic colorectal cancer are shown in Table 1. Although CRC during pregnancy is often diagnosed at a more advanced stage, patient survival has been reported to be comparable with that in nonpregnant patients.[19,21] The risks for the child include teratogenic effects or growth retardation. We present a case report of a patient diagnosed with metastatic CRC receiving chemotherapy during pregnancy.

Case Report

A 43-year-old woman, 23 weeks pregnant with her second child after in vitro fertilization, presented with rectal bleeding and mucus, diffuse left-sided abdominal pain, and reduced general condition.

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Table 1 Published Case Reports of Treatment with a FOLFOX Regimen During Pregnancy in Patients With Metastatic Colorectal Cancer

First Author (year)	Diagnosis	Chemotherapy	Gestational week	Delivery (weeks)	Fetal Outcome	Follow- up
Gensheimer (2009)[13]	Metastatic rectal cancer	FOLFOX	20	33	Healthy child	3 years
Kanate (2009)[12]	Metastatic rectosigmoid cancer	FOLFOX	NR	31.5	Hypothyroid	1 year
Jeppesen (2011)[10]	Metastatic colon cancer	FOLFOX	13	33	Healthy twins	2 years
Dogan (2013)[11]	Metastatic rectal cancer	FOLFOX	NR	36	Small for gestational age	10 months
Makoshi (2015)[14]	Metastatic colon cancer	FOLFOX	22	38	Healthy child	2 years
Robson (2017)[15]	Metastatic rectosigmoid cancer	FOLFOX	2nd trimester	34	Healthy child	NR
Robson (2017)[15]	Metastatic colon cancer	FOLFOX	2nd trimester	—	Intrauterine fetal loss gestational week 33	—
Lee (2019)[17]	Metastatic colon cancer	FOLFOX	20	33	Still birth	31 months
Lee (2019)[17]	Metastatic colon cancer	FOLFOX	23	36	Healthy child	1 year

Abbreviation: NR = not reported.

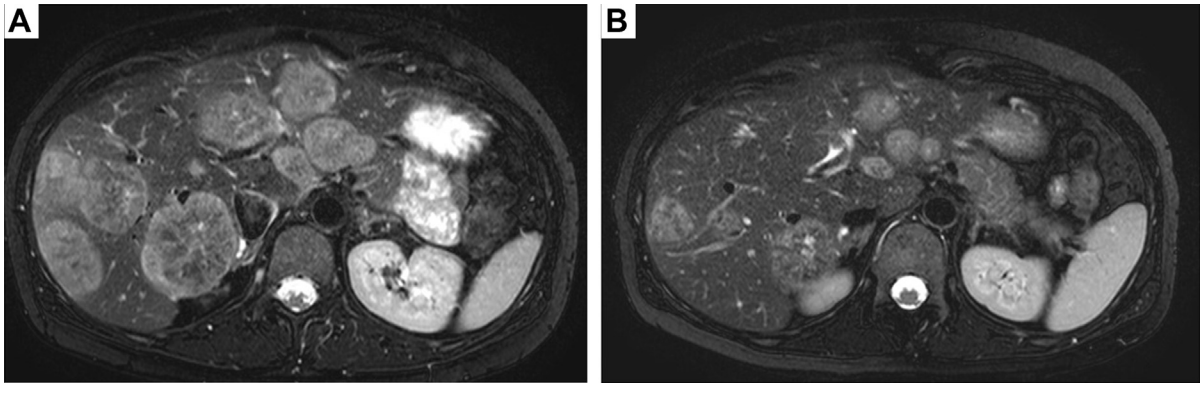
Colonoscopy revealed a nonobstructing tumour in the sigmoid colon, comprising two-thirds of the circumference. Biopsy of the tumour revealed a moderately to poorly differentiated adenocarcinoma, no microsatellite instability, with *NRAS* mutation, *KRAS* and *BRAF* wild type. A computed tomography (CT) scan of the thorax and upper abdomen showed 23 liver metastases and a small unspecific lung nodule. Magnetic resonance imaging (MRI) of the liver showed multiple metastases in all liver segments, the largest 60 mm in diameter (Figure 1A). A pelvic MRI showed a 7-cm-long sigmoid tumour, regional lymph node metastases and vessel invasion, but no extraregional metastases. Carcinoembryonic antigen was elevated to 64.7 μg/L, hemoglobin was 10.3 g/dL, and aspartate transaminase was 77 U/L; otherwise, laboratory tests were mostly normal, including the white blood cell count and alkaline phosphatase.

The case was discussed in a specially composed multidisciplinary team meeting with a colorectal surgeon, obstetrician, oncologist, and neonatologist. Because the patient continued to have bowel movements, upfront surgical resection of the primary tumour was not deemed to be necessary. Owing to multiple liver metastases in all segments, palliative combination chemotherapy was recommended, and delay of chemotherapy until delivery was not considered to be possible. The hepatobiliary multidisciplinary team concurred with nonresectability of the liver metastases. The patient and her husband were thoroughly informed of the cancer diagnosis and stage, the noncurative intent of the treatment, the rationale for the treatment recommendation, and risk considerations for the patient and fetus. She consented to receive chemotherapy during pregnancy.

She started chemotherapy with modified FOLFOX-6 in full dose in week 26 of her pregnancy, given with oxaliplatin 85 mg/m^2, calcium folinate 400 mg/m^2, 5-FU 400 mg/m^2 day 1, and 5-FU 2400 mg/m^2 in a 48-hour infusion. Ondansetron and hydrocortisone were given as antiemetics. After 2 cycles of FOLFOX, an MRI showed size reduction of all liver metastases, the largest measuring 40 mm. Chemotherapy was well-tolerated by the patient, with no serious adverse effects, and FOLFOX was continued without dose reductions or delays. After 2 additional FOLFOX cycles, MRI showed further tumour regression, the largest metastasis measured 23 mm (Figure 1B); the serum carcinoembryonic antigen level had decreased to 6.3 μg/L.

The patient had regular follow-up by a senior obstetrician almost weekly from the time of cancer diagnosis and throughout

Figure 1 MRI of Liver (A) at Start of Chemotherapy and (B) After 4 Cycles of FOLFOX



pregnancy. Ultrasound examination showed normal growth and development of the baby, with no signs of placental insufficiency. The patient's medical condition was considered good during the whole pregnancy. The child was delivered by an elective caesarean section in gestational week 34. The recommendation for early delivery was related to her cancer diagnosis and a high psychological burden related to the pregnancy and metastatic disease. After delivery, she received medication to suppress lactation. The child was healthy with birth weight according to gestational age, and was admitted to the neonatal intensive care for a few days, and discharged from hospital after a week.

During the caesarean procedure, a colorectal surgeon examined the abdomen and sigmoid tumor, and no signs of macroscopic lymph node metastases or peritoneal carcinomatosis were observed. After delivery, a CT scan revealed no further metastases. Owing to good treatment response and tolerability, FOLFOX was resumed 4 weeks after delivery. After 4 cycles of FOLFOX, with further partial response, she underwent a laparoscopic sigmoid resection with colostomy. Pathology examination revealed no residual tumour, ypT0N0. Chemotherapy was continued, and owing to exceptionally good response, she underwent left-sided hemihepatectomy with additional resections and ablations, including the removal of 20 lesions. Later she underwent resection for 4 remnant lesions and a wedge resection of a solitary lung metastasis. Currently, she has relapsed, with metastases to the liver and abdominal lymph nodes and is receiving chemotherapy. The child is 3 years old, and the patient reports that the child attends routine follow-up in a Child Health Centre, and is developing adequately according to age.

Discussion

To aid in difficult treatment decisions, case reports and literature reviews prove helpful. There are a few case reports of chemotherapy for CRC during pregnancy.[10-18,22,23] Most of these patients have received 5-FU and oxaliplatin in the second or third trimester with reasonable treatment efficacy and safety.[10-15] Overviews of the challenges of chemotherapy during pregnancy provide valuable guidance.[8,19,20] Because the patient's need for treatment contrasts with the child's challenges by being prematurely delivered, interdisciplinary cooperation is necessary, including surgeons, oncologists, and obstetricians.

For cancer during pregnancy in general, the European Society for Medical Oncology clinical practice guidelines advice that chemotherapy should not be administered during the first trimester.[24] In the second and third trimesters in general, chemotherapy can be considered, with a small risk of teratogenic effects and intrauterine growth restriction. A comprehensive review of chemotherapy for CRC discussed the different drugs in detail and reported on outcomes and safety of published case reports.[8] A monograph on the developmental effects and pregnancy outcomes associated with chemotherapy during pregnancy reports on several individual chemotherapeutics.[25] These publications, along with the case reports, were valuable for guiding the treatment decision of the reported patient, who started chemotherapy with a FOLFOX regimen toward the end of the second trimester. The publications provided documentation of patients receiving 5-FU, and FOLFOX, and a few reports on irinotecan. Growth factors such as epidermal growth factor and vascular endothelial growth factor are of importance for fetal growth and maintenance of pregnancy, and there is a lack of reports on human exposure; therefore, treatment with monoclonal antibodies against epidermal growth factor receptor or vascular endothelial growth factor should be avoided during pregnancy.[8,25] A recent review suggests treatment algorithms of surgery and chemotherapy for CRC in pregnancy.[19] The International Network on Cancer, Infertility and Pregnancy[26] database has reported 41 patients with CRC during pregnancy; 12 received chemotherapy during the second or third trimester of pregnancy.[18] Chemotherapy was given with 5-FU or FOLFOX, all patients delivered live children, of these 4 were small for gestational age and 1 had a congenital malformation of leg length discrepancy.[18]

To our knowledge, there are no data available regarding safety of treatment with FOLFOX during breast feeding. In general, breast feeding is not recommended until at least 2-4 weeks after the completion of systemic chemotherapy.[27] Our patient was recommended to suppress lactation and did not breast feed because chemotherapy was continued after delivery.

Pregnancy also poses diagnostic challenges. In general, CT scans and positron emission tomography scans should be avoided.[24] MRI is a preferred modality for diagnosis and evaluation of liver metastasis during pregnancy to avoid radiation to the fetus. An MRI should be performed with diffusion-weighted as well as T2- and T1-weighted images, without a contrast agent.[28] For detection of lung metastasis, a low-dose CT scan of the thorax without a contrast agent provides sufficient diagnostic information. We used MRI for evaluation of initial disease extent, and together with serum carcinoembryonic antigen level for evaluation of treatment response to chemotherapy.

It has been suggested that CRC may be aggressive owing to factors during pregnancy, and respond well to treatment after delivery.[29] This assumption was not confirmed in a population-based study from California,[21] where no survival difference was observed between pregnant and nonpregnant women with CRC. Also, suggestions that estrogen or fertility treatment may affect the risk of colorectal cancer has to our knowledge not been confirmed.[30-32] In the post partum period, aggressive cancer treatment, including surgery for liver metastases, should be considered.[15] Our patient had an exceptionally good response to chemotherapy, with pathologic complete response of the primary tumour, and conversion to resectable liver metastases. We suggest that all available therapeutic options should be considered to increase the possibility of curative treatment and to prolong survival. It is encouraged to report cases by publishing or entering them in international databases.[25,26]

Conclusion

We present a case report of metastatic CRC during pregnancy, treated with FOLFOX chemotherapy during the third trimester with good efficacy. The child was healthy according to gestational age. After delivery, the patient continued chemotherapy and underwent surgery.

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Written informed consent was obtained from the patient and her husband for publication of this case report and images. The manuscript has been approved by the patient.

Disclosure

The authors have stated that they have no conflicts of interest.

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