FOLFOXIRI in Pregnant Women with Colorectal Cancer: A Case Report and Review of the Literature

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Abstract
Colorectal cancer (CRC) in pregnancy is rare and often presents at a late stage due to the masking of signs by pregnancy. A typical chemotherapeutic regimen for stage III and IV CRC comprised 5-Fluorouracil (5-FU) and oxaliplatin. The treatment of CRC during pregnancy is complicated owing to the potential risk of teratogenicity with chemotherapy, especially in the first trimester. Data suggest that the administration of chemotherapy beyond the first trimester may be relatively safe. Previous reports have shown success with the use of FOLFOX (folinic acid, 5-FU, oxaliplatin) and FOLFIRI (folinic acid, 5-FU, irinotecan) during pregnancy. Moreover, neoadjuvant FOLFOXIRI (folinic acid, 5-FU, oxaliplatin, irinotecan) resulted in improved outcomes when compared to standard preoperative chemoradiotherapy in the treatment of locally advanced and metastatic CRC. The use of FOLFOXIRI in pregnancy is not currently documented, and therefore, the outcomes of using this chemotherapeutic regimen are unclear. The aim of this case report was to demonstrate the use of FOLFOXIRI in pregnancy. A retrospective chart review was performed to assess the clinical course and fetal outcome of 2 patients presented in this case report. FOLFOXIRI was initiated in two pregnant women with nonmetastatic and metastatic CRC, resulting in successful delivery of healthy infants. FOLFOXIRI is an effective chemotherapy regimen for the treatment of advanced CRC and may be used during the second and third trimesters of pregnancy.
Introduction

Colorectal cancer (CRC) during pregnancy is rare and occurs in one out of 13,000 pregnancies [1]. Chemotherapy regimens containing 5-fluorouracil (5-FU) and oxaliplatin comprise the standard approach to systemic treatment for the American Joint Committee on Cancer (AJCC) Stage III and Stage IV CRC. The combination of folinic acid, 5-FU, oxaliplatin, and irinotecan (FOLFOXIRI), in particular, is an active chemotherapy triplet commonly utilized for the treatment of metastatic CRC [2]. In the setting of pregnancy, however, this pharmacotherapy may pose a potentially high risk of teratogenicity in the first trimester, but there is an absence of data regarding its safety and efficacy in pregnant women with this condition [3, 4]. This case report includes two pregnant women who, after being diagnosed with locally advanced and metastatic CRC and treated with FOLFOXIRI, went on to deliver viable, healthy infants.

Case 1

A 36-year-old G2P1001 woman presented at 24 weeks gestation with constipation and rectal bleeding. Her past medical history was notable for dyslipidemia, chronic constipation, and hemorrhoids, which improved transiently with fiber, laxative therapy, and dietary modifications. However, her constipation worsened, and became recalcitrant to medical therapy. She continued to have rectal bleeding and constipation associated with a 35-lb weight loss over 5 months. At 10 weeks gestation, she was found to have symptomatic anemia, with a hemoglobin level of 7.4 g/dL, and she received a blood transfusion in the emergency department (ED).

She was referred to the gastroenterology clinic for the evaluation of her anemia. She endorsed persistent tenesmus, constipation, and daily bloody stools. Her medications included only the aforementioned laxatives and an iron supplement. She rarely consumed alcohol and denied tobacco or illicit drug use. Physical examination was notable for diminutive external hemorrhoids and an unremarkable digital rectal exam. An urgent colonoscopy revealed a circumferential mass in the rectum, with biopsy confirming a moderately differentiated adenocarcinoma consistent with a rectal primary tumor (shown in Fig. 1). The cancer was negative for MLH1, MSH2, MSH6, and PMS2 mismatch repair protein abnormalities by immunohistochemistry. Subsequent MRI of the abdomen and pelvis demonstrated a large rectal tumor with an inferior margin of 3.5 cm superior to the anal verge (shown in Fig. 2), and multiple perirectal and presacral nodules. There were two liver masses with imaging characteristics most suspi-

Fig. 1. Moderately differentiated adenocarcinoma with a decrease in nuclear polarity and irregular tubule formation (red arrow) in addition to necrosis (yellow arrow).
cious for metastases. A CT scan of the chest demonstrated six pulmonary nodules suspicious for malignancy as well. The malignancy was initially staged as cTxNxM1.

After consultation with maternal-fetal medicine and medical oncology, the patient desired to continue her pregnancy and was started on chemotherapy with FOLFOXIRI at 25 weeks gestation. Her rectal bleeding slowed significantly, and her pain diminished within 2 weeks of starting treatment. Her pregnancy was complicated by intrauterine growth restriction, measured by low abdominal circumference at the end of week 33 of gestation. Two antenatal doses of betamethasone were administered in anticipation for early induction. Labor was induced in week 34, and she successfully delivered vaginally without complication. The infant demonstrated Apgar scores of 8 and 9 at 1 and 5 min, respectively. While the infant was small for gestational age (5th percentile by weight), there were no congenital malformations. There was mild neutropenia, with an absolute neutrophil count of 1.18 × 10^3 cells/μL, elevated serum creatinine of 1.2 mg/dL, and mild jaundice of prematurity that resolved quickly with the administration of intravenous fluids and oral feeding. At her first routine wellness visit, the child was without any documented problems or developmental delays and remained well at her 6-year routine exam. The patient has since undergone treatment for her metastatic disease with systemic therapy and palliative local procedures.

Case 2

A 31-year-old, previously healthy woman, G5P3013, at 14 weeks gestation presented to the ED with worsening intermittent constipation, low back pain, and rectal bleeding that began 6 months prior. Of note, her constipation was previously treated with laxatives, enemas, and manual disimpaction. A CT scan had been performed 2 months prior to this presentation during a previous ED visit, which was notable for colonic wall thickening, and she was subsequently treated with ciprofloxacin and metronidazole for presumed colitis without improvement in her symptoms. She was referred to gastroenterology at that time, with plans for an upper endoscopy and colonoscopy to further evaluate the cause of rectal bleeding. However, when the patient discovered she was pregnant, this was postponed by the physician who intended to resume the workup after pregnancy.
At this presentation, the patient denied nausea, vomiting, hematemesis, or melena. She endorsed a decreased appetite and greater than 20 lb weight loss over the prior 3 months. Her past medical history included a miscarriage 7 months prior to this presentation but was otherwise unremarkable. Her medications included occasional acetaminophen. She denied a family history of cancer or consumption of alcohol, tobacco products, or illicit drugs. Physical examination revealed a soft, nontender, nondistended abdomen without palpable masses. A digital rectal exam revealed a firm, circumferential mass palpated at 4–5 cm from the anal verge.

The patient was referred to gastroenterology again and underwent a colonoscopy that confirmed the finding of a fungating, partially obstructing, 8-cm mass in the rectum, 4–5 cm from the anal verge. The pathology report confirmed a poorly differentiated adenocarcinoma with signet ring cells (shown in Fig. 3). The cancer was negative for MLH1, MSH2, MSH6, and PMS2 mismatch repair protein abnormalities by immunohistochemistry. A CT scan of the chest and abdomen did not show metastases. A pelvic MRI showed several enlarged lymph nodes adjacent to the tumor (shown in Fig. 4), suspicious for nodal metastasis. The malignancy was staged as cT3N2M0.

After a discussion with the medical oncologist over the risks and benefits of pursuing treatment, the patient wished to continue the pregnancy. Because of the severity of her...
symptoms, she was started on neoadjuvant FOLFOXIRI with a goal of decreasing tumor bulk. The patient endorsed less abdominal pain and rectal bleeding 4 weeks following initiation of chemotherapy. A short interval follow-up pelvic MRI after 1 month of chemotherapy showed stable disease. Eight cycles of FOLFOXIRI were completed at 30 weeks of gestation. Follow-up pelvic MRI at that time again showed stable disease.

At regular antepartum visits with the obstetricians and maternal-fetal medicine specialists, there were concerns for impending oligohydramnios. Serial ultrasound exams following this revealed low-normal amniotic fluid levels in addition to the normal length of the fetus and weight in the 33rd percentile for gestational age. Two antenatal doses of betamethasone were administered in anticipation for induction. Labor was induced at 32-weeks, and spontaneous vaginal delivery was successfully achieved. The infant demonstrated Apgar scores of 8 and 9 at 1 and 5 min, respectively. No peripartum complications occurred in the mother. While the child did exhibit some feeding difficulty and mild hypertonicity at birth, there were no other observed deficits or congenital malformations. At 9-week follow-up, the child’s hypertonicity and feeding difficulties had resolved, and development was appropriate for the child’s age as recent as 6 months of age.

**Discussion**

CRC in pregnancy is likely to become more common as women elect to delay pregnancy late into their 3rd and 4th decades of life [5]. Furthermore, the incidence of CRC is increasing in younger adults [6]. CRC in pregnancy is often complicated by the late stage of diagnosis, due to vague symptoms and masking of the symptoms by pregnancy [1]. Additionally, the possibility of fetal harm may sometimes discourage clinicians from pursuing a diagnostic workup and could conceivably contribute to a delay in diagnosis [7]. Diagnosis at an advanced stage further increases the risk for complications, such as obstruction, perforation, or hemorrhage [7]. Both patients in this case report were greater than 30 years of age at diagnosis and presented with vague gastrointestinal symptoms which were refractory to initial therapy, leading to complications of chronic blood loss anemia, tenesmus, and partial bowel obstruction.

Treatment decisions for CRC in pregnant women are dependent on a number of factors, which include fetal gestational age, tumor location, stage, and potential risks to the mother and the fetus. The treatment plan may include surgery or chemotherapy and should be tailored to the patient’s unique clinical scenario and preferences. If the cancer is diagnosed at an early gestational age, termination of pregnancy may be recommended to expedite therapy. Alternatively, termination may be deferred as long as the mother understands and accepts the risk of disease progression [7].

The risk of chemotherapy is dependent on fetal gestational age [8]. Exposure to chemotherapy in the first trimester poses the greatest risk for teratogenicity, with an incidence of spontaneous abortions or malformations of up to 15–25% [3]. However, in some cases of metastatic CRC, chemotherapy may be considered in early pregnancy to reduce tumor burden and allow the fetus to reach a viable gestational age [3]. In these situations, the patient must understand the potential palliative intent balanced with the potential risk of harm to the fetus [7]. In the second or third trimesters, chemotherapy is generally safer but is associated with an increased incidence of small for gestational age fetuses [9]. While many chemotherapeutic agents have demonstrated significant harm to fetal health when administered during the first trimester of pregnancy, relative safety has been demonstrated when given in the second and third trimesters [10, 11]. Based on these findings, the European Society of Medical Oncology recommends chemotherapy to be avoided in early pregnancy [12].
The patients in this case report received FOLFOXIRI. 5-FU functions as a pyrimidine analog, disrupting thymidine synthase. The human safety of 5-FU has been scrutinized retrospectively in over 178 pregnancies, through a literature review of case reports, case series, and surveys [10]. In utero exposure was associated with a 1% overall rate of major malformations when chemotherapy was administered during the second or third trimester, which was not significantly different from the rate in the general population. Platinum-based therapies, such as oxaliplatin, have also been associated with relatively safe fetal outcomes when administered in the second and third trimesters, with agents such as cisplatin and carboplatin demonstrating rates of major fetal malformation of 1% and 0%, respectively [10]. Oxaliplatin has been associated with an increased incidence of small for gestational age [9]. Among 4 patients registered in the International Network on Cancer, Infertility, and Pregnancy database who received combination FOLFOX treatment in the second or third trimesters, all four delivered viable infants without congenital malformations [3]. Finally, two reports of irinotecan administered during the second trimester did not note any complications or malformations [13, 14].

Chemotherapy is often continued until a gestational age of 35 weeks or 3 weeks before the expected due date [7]. This is recommended so as to avoid the increased risk of chemotherapy-related complications, such as bone marrow suppression, hemorrhage, and maternal and fetal death during delivery [5, 15]. In this case report, 1 patient began chemotherapy in the early second trimester, while the other started in the late second trimester. Labor was induced at the 34th and 32nd weeks in patient 1 and patient 2, respectively, to time the delivery with cessation of chemotherapy and to minimize the break from treatment. Both patients were given at least a 2-week chemotherapy-free interval prior to delivery for bone marrow recovery. Patient 1 resumed chemotherapy in the postpartum period, while patient two went on to proceed with combined chemoradiation therapy.

There have been numerous case reports of pregnant women with metastatic CRC receiving combination chemotherapy with FOLFOX or FOLFIRI [3, 5]. However, to our knowledge, there have been no reports of using FOLFOXIRI in pregnant women with metastatic and nonmetastatic CRC. The PRODIGE-23 trial found that neoadjuvant therapy with a modified regimen of FOLFOXIRI (mFOLFIRINOX) for localized rectal cancer resulted in longer disease-free survival and metastasis-free survival when compared to standard preoperative chemoradiotherapy [16]. A meta-analysis demonstrated that FOLFOXIRI resulted in superior progression-free survival, overall survival rates, and overall response rates in metastatic CRC compared to oxaliplatin- or irinotecan-based first-line therapy, despite higher rates of neuro- and bone-marrow toxicity [17]. Given the effectiveness of combination regimens, and FOLFOXIRI, in particular, it should be considered in pregnant women. Understandably, there is concern that the use of three teratogenic agents may increase the risk for congenital malformations and other neonatal abnormalities. However, due to the rare occurrence of CRC in pregnancy, there is a lack of data to draw any definitive conclusions on this risk.

**Conclusion**

CRC in pregnancy is exceedingly rare. Much of what is known about the management of this condition comes from case reports. FOLFOXIRI is a preferred treatment for CRC, but its use in pregnancy has not been previously reported. We present 2 patients with advanced CRC who were treated with FOLFOXIRI in the 14th and 25th weeks of gestation. Both women experienced significant symptomatic improvement from treatment and were able to continue their pregnancies without any unexpected adverse events. They delivered healthy infants in the 32nd and 34th week of pregnancy, respectively. At follow-up, both children were doing...
well without congenital abnormalities or other adverse effects from intrauterine exposure to chemotherapy.

Statement of Ethics

This study protocol was reviewed and approved by The Queen’s Medical Center Research and Institutional Review Committee, approval number RA-2021-056. The aforementioned committee also approved a waiver of the need of written informed consent for both of the patients to publish the case report and any accompanying images and a waiver of HIPAA authorization for this study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors, including Landon Kozai, Kevin Benavente, Adham Obeidat, and Jared Acoba contributed to this work in the process of data acquisition, drafting of the manuscript, and critically revising the manuscript. All authors approve of the final version of the manuscript for publication.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants. Further inquiries can be directed to the corresponding author Landon Kozai.

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