Oncology Case Reports Journal

Case Series
Published: 02 Aug, 2024

Systemic Treatment of Metastatic Gastrointestinal Cancer in Pregnancy - Two Case Reports and A Short Review

*Meschede J[1], Kunze M[1], Bertz H[2], Juhasz-Boess I[1] and Markfeld-Erol F[1]**

[1]Department of Obstetrics and Gynecology, University of Freiburg Medical Center, Germany

[2]Division of Hematology, Oncology and Stem Cell Transplantation, University of Freiburg Medical Center, Germany

Abstract

There is a clear need for more experience in the treatment of pregnant patients with metastatic gastrointestinal cancer. We present our experiences with two women diagnosed with metastatic disease during pregnancy.

A 29-year-old I/O was diagnosed with metastatic colorectal cancer in the 12th week of pregnancy. She underwent systemic therapy with FOLFOX (oxaliplatin/5-fluorouracil) in the second trimester because of a high tumor burden. The treatment improved her general condition significantly. She delivered a healthy boy at 36 weeks of gestation.

The second case is as follows: A 32-year-old I/O suffered from advanced gastric carcinoma and was diagnosed in the second trimester. She received FOLFOX, which was initiated in the 22nd week of pregnancy. She delivered a healthy girl in the 36th week *via* emergency caesarean section due to an abruptio placenta during labor. The management of cancer in pregnant women is challenging and requires a multidisciplinary approach.

We conducted a thorough review of the literature before initiating the treatment.

The purpose of this article is to provide a brief overview of the current data for FOLFOX chemotherapy in pregnancy.

Keywords: Metastatic colorectal cancer; Pregnancy; FOLFOX; Chemotherapy

OPEN ACCESS

Correspondence:
Filiz Markfeld Erol, Department of Obstetrics and Gynecology, University of Freiburg Medical Center, Germany,

Received Date: *11 Jul 2024*
Accepted Date: *26 Jul 2024*
Published Date: *02 Aug 2024*

Citation:
Meschede J, Kunze M, Bertz H, Juhasz-Boess I, Markfeld-Erol F. Systemic Treatment of Metastatic Gastrointestinal Cancer in Pregnancy - Two Case Reports and A Short Review. Oncol Case Report J. 2024; 7(1): 1063.

ISSN: 2641-9173

Case Series

Case 1

The first patient was a 29-years-old woman who was diagnosed with metastatic colorectal cancer in pregnancy. At 27, the patient developed locally advanced colorectal cancer after battling ulcerative colitis for years. She underwent surgical treatment initially, including a proctocolectomy with local lymph node dissection. The pathological staging was pT4b, pN2b, cM0, G2. She then underwent 12 cycles of adjuvant chemotherapy with FOLFOX (oxaliplatin, folic acid, and 5-fluorouracil). One year and two months later, the patient became pregnant.

In the 12th week of gestation, a follow-up examination revealed the presence of metastasis. The MRI scan definitively showed a paraaortic lymph node and a solitary hepatic metastasis. The patient was scheduled for a tumor resection at an external hospital in the 15th week of gestation.

The surgery was a success. We achieved a clinical R0 resection of the hepatic metastasis and the bulky paraaortic lymph nodes. However, the resection margin was very narrow on pathological examination.

Despite the need for chemotherapy, the patient did not receive any adjuvant systemic treatment during her pregnancy.

Three weeks after surgery, the patient developed ascites. The patient's condition rapidly deteriorated, with the diagnosis of progressive disease. She suffered from abdominal pain and nausea and was unable to eat properly.

At 26 weeks of gestation, the patient was transferred to our institution.

She was hospitalized and received adequate pain treatment. She also underwent a re-staging *via* MRI (Figure 1A, 1B). The abdominal scan revealed multiple hepatic metastases, peritoneal

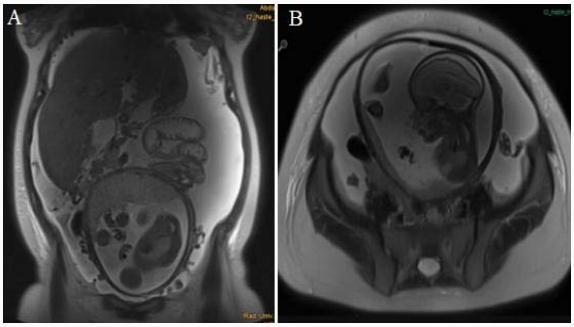

Figure 1: MRI scan at 26 weeks of pregnancy shows the pregnant uterus with the umbilical cord, but also the ascites (Figure 1A+1B) and the liver metastasis (Figure 1A).

carcinosis, extensive ascites, and multiple metastatic lymph nodes.

The case was discussed in an interdisciplinary tumor conference with experts from the departments of radiology, obstetrics, and oncology. The different disciplines reviewed the literature and we decided to recommend a re-induction with FOLFOX chemotherapy. The patient was informed of the risks and consented to the treatment.

At 28 weeks of gestation, she began the first of four scheduled cycles of chemotherapy. The treatment was well tolerated and the symptoms were reduced rapidly. The pregnancy was monitored frequently and the fetus showed continual growth, normal amniotic fluid, and Doppler sonography without pathological findings.

The last cycle of therapy was administered in the 32nd week of pregnancy. Three weeks later, we started to induce labor.

The patient gave birth to a healthy boy with a good Apgar score and a weight of 2,950 gr. The newborn adapted without any difficulties. He did not require admission to the NICU. The mother was able to breastfeed her son until the chemotherapy was restarted. The pediatric examination revealed no abnormalities.

After delivery, the patient underwent another MRI scan, which revealed a mixed response. The ascites, liver metastasis, and parts of the peritoneal carcinosis regressed, but some of the tumor nodes next to the uterus progressed. Therefore, the therapy was changed to FOLFIRI and Panitumumab (EGFR receptor antagonist).

After four cycles of treatment, the patient showed progressive disease. The chemotherapy was changed to FOLFOX and bevacizumab for another eight cycles.

After the tumor progressed under that treatment, we started Lonsurf (trifluridine/tipiracil) therapy.

The patient's condition continued to deteriorate, and she died 10 months after the delivery of her son.

Case 2

A 32-year-old primipara presented in the 11th week of pregnancy with obstructive uropathy in an external hospital with acute postrenal kidney failure and urinary tract infection. She received antibiotic treatment and a pigtail catheter on the left side, two weeks later a pigtail catheter was placed on the contralateral side for the same problem. Given the insufficient effect of the previous procedure and ongoing complaints, she underwent bilateral percutaneous nephrostomy.

MRI imaging was performed in the 16th and 18th weeks. The radiologists diagnosed retroperitoneal fibrosis and an augmentation of soft tissue with bilateral compression of both ureters, bilateral pleural effusions, and ascites. It was assumed that the patient had an autoimmune disorder, namely Morbus Ormond.

In the 20th week of pregnancy, the patient became more symptomatic with dyspnea and abdominal pain. She was transferred to our hospital. A Matthys catheter was placed in the left thorax due to the pleural effusion and a total of 1,800 ml was drained. Furthermore, a peritoneal catheter was inserted. Both body fluids were subjected to a cytologic analysis. The two samples both showed malignant cells, and the immunohistochemical pattern indicated a tumor of the upper gastrointestinal tract.

A CT scan of the thorax definitively showed carcinosis of the pleura and a pulmonary mass in the right inferior lobe. A laparoscopy and a cystoscopy were performed to confirm the diagnosis. The procedure revealed the presence of an omental cake, peritoneal carcinosis, and bladder infiltration. Furthermore, the patient underwent a gastroscopy, which successfully identified the primary tumor.

The pathological report confirmed an adenocarcinoma (mixed type: Diffuse and intestinal type), Her-2 negative, estrogen and progesterone receptor negative, PDL-1 Score +1, and human papillomavirus 16 positive.

The case of the patient was discussed in the interdisciplinary tumor board and a systemic therapy with FOLFOX was recommended. The patient was informed that termination of pregnancy was also a possibility due to her poor prognosis and her very impaired physical condition. However, the patient decided to continue the pregnancy.

At 22 weeks pregnant, the patient began chemotherapy with FOLFOX.

During the six cycles of chemotherapy, she suffered from a small and subacute infarction in the pons and a deep vein thrombosis on the left leg.

The pregnancy was monitored by ultrasound and cardiotocography every two weeks in the department of obstetrics.

The fetus showed clear signs of intrauterine growth retardation under chemotherapy. Despite the flattening of the growth curve, the Doppler in the umbilical artery and the middle cerebral artery remained within the normal range.

The patient's general condition improved significantly during treatment, as evidenced by the MRI scan after four cycles, which showed a good response. The ascites and pleural effusions also regressed.

At 35+3 weeks of pregnancy, it was decided to induce labor due to the intrauterine growth retardation and the relative maturity of the fetus. The last cycle of FOLFOX was applied three weeks prior. During labor, the fetal heart rate suddenly dropped and vaginal bleeding occurred. Abruption of the placenta was assumed. Therefore, an emergency cesarean section was performed.

During surgery, the abruption of the placenta was confirmed, and the fetus was delivered after 7 min.

The child weighed 1,700 gr, had a pH of 7.05 with a BE of -5.3 mmol/L, and an APGAR score of 4/6/8. After three days in the

intensive care unit, the girl was transferred to her mother.

Eight days after delivery, another MRI scan definitively showed progressive disease with liver lesions, progressive peritoneal carcinosis, bulky nodes, bone metastasis, and an intrahepatic cholestasis.

Immediately following delivery, the patient began a course of chemotherapy with FOLFOX, which was continued for three additional cycles. Imaging results demonstrated that the disease remained stable. Subsequently, the treatment was changed to pembrolizumab and FLOT. After two cycles, the patient became septic, so antibiotic treatment was initiated. The patient's tumor grew rapidly and she died three months after delivery.

Discussion

It is extremely rare for Colorectal cancer and Gastric cancer to occur in pregnancy. The incidence of colorectal cancer in pregnancy is reported to be 1:1300 in the literature [1,2]. It is estimated that gastric cancer occurs in 1:3800 to 1:1000 pregnancies [3].

Malignant tumors of the breast, ovaries, cervix, thyroid, and hematopoietic system are more common. Systemic treatment of gastrointestinal tumors includes different cytostatic agents and antibodies with proven efficacy. However, there is a dearth of experience regarding the effects on the fetus during pregnancy.

The decision to administer cytotoxic treatment to pregnant patients must be made after a thorough discussion with the patient and her family. The following questions must be answered: Further delay of the treatment would have been unjustifiable given the patients' alarming condition. During treatment, it is crucial to assess whether the treatment's aims remain realistic in light of potential side effects for the mother and fetus, particularly in a metastatic situation. The question of fetal impact is more complex and fundamentally depends on the trimester of pregnancy at which therapy begins.

The first 12 weeks of pregnancy are the most vulnerable time for physical malformations.

In the second trimester, chemotherapy can cause intrauterine growth retardation, myelosuppression in the fetus, small for gestational age fetuses, and functional defects.

In our cases, we intend to use 5-Fluouracil, an antimetabolite. The data from the US National Toxicology Program clearly shows that 5-FU crosses the placenta and has a high teratogenic potential when administered in the first trimester. In fact, 31% of the cases resulted in malformations (4/13). The investigation also demonstrated that the administration in the second and third trimesters has a very low risk for malformations. In fact, the incidence of club foot and hemihypertrophy of the lower extremity is only 1% to 2% (2/161, 6). Other complications were reported, including growth retardation (2/171), reduction of the amniotic fluid (2/171), spontaneous preterm labor (5/171), and small for gestational age (5/171). Respiratory distress was also described, but mainly caused by iatrogenic preterm birth.

The other cytostatic substance the patient received was Oxaliplatin, a third-generation platinum agent with a rather low molecular weight. This indicates an exposure to the fetus in the pregnancy. We have more data about the effects of platinum-based chemotherapy for cisplatin. The study by Song et al. revealed that cisplatin caused mild elevation in serum creatinine (1/88 exposed fetuses), anemia (1/88), severe bilateral perceptive hearing loss (1/88), and 2 of 88 children developed malignant tumors (1 with embryonal rhabdomyosarcoma at the age of 5 years and 1 with acute myeloid leukemia at the age of 2 years) [4].

Rogers et al. reported seven cases of patients who received FOLFOX chemotherapy for colorectal cancer. Five of those patients were treated in the second trimester, one patient started at 13 weeks of gestation, and one at 29 weeks. One case of hypothyroidism was reported [1,5-8]. The other children were healthy apart from two SGA fetuses [1].

The data on FOLFOX chemotherapy in the second trimester of pregnancy is limited, but the studies show that the risk to the fetus is tolerable. There is a clear risk of intrauterine growth retardation, and it is reasonable to monitor the fetus for this [9].

In cases of metastatic colorectal cancer, treatment often contains anti-angiogenic substances, such as anti-Vascular Endothelial Growth Factor antibodies (VEGF), like bevacizumab, Ziv-aflibercept, ramucirumab, and regorafenib [1,10-12].

It is contraindicated to use these substances in any stage of pregnancy. Animal studies have shown severe teratogenic effects, including skeletal deformations, growth restrictions for bevacizumab, external, visceral, and skeletal malformations for Ziv-aflibercept, and multiple deformations for regorafenib. Therefore, an anti-VEGF targeted therapy is definitely not an option in pregnancy.

Another therapeutic option is anti-Epithelial Growth Factor antibodies (EGF), like cetuximab and panitumumab. However, animal studies also showed similarly serious effects as the anti-VEGF agents. There is no experience in human pregnancy because the animal model on monkeys showed an increased rate of abortions and intrauterine deaths [13,14].

In summary, treatment with anti-VEGF or anti-EGF targeted substances should be avoided in pregnancy.

It is imperative that the running chemotherapy be interrupted at least two to three weeks before delivery to avoid myelosuppressive side effects for the newborn. Side effects like thrombocytopenia or leukopenia of the fetus under labor can cause intracerebral bleedings or favor severe neonatal postpartum sepsis [15-17].

Summary

The treatment of patients with metastatic gastrointestinal cancer during pregnancy is challenging. However, the data and our case demonstrate that FOLFOX chemotherapy is a reasonable therapeutic option when administered in the second trimester. Anti-VEGF and anti-EGF antibodies are contraindicated at all stages of pregnancy. For patients with a high tumor burden and severe tumor-related symptoms, FOLFOX chemotherapy can improve the patient's quality of life. The fetus must be monitored closely, especially for the risk of intrauterine growth restriction. The treatment should be stopped at least 2 to 3 weeks before delivery to avoid hematotoxic side effects for the fetus.

References

1. Rogers JE, Dasari A, Eng C. The treatment of colorectal cancer during pregnancy: Cytotoxic chemotherapy and targeted therapy challenges. Oncologist. 2016;21(5):563-70.

2. Salani R, Billingsley CC, Crafton SM. Cancer and pregnancy: An overview for obstetricians and gynecologists. Am J Obstet Gynecol. 2014;211(1):7-14.

3. Maggen C, Lok CA, Cardonick E, van Gerwen M, Ottevanger PB, Boere IA, et al. Gastric cancer during pregnancy: A report on 13 cases and review of the literature with focus on chemotherapy during pregnancy. Acta Obstet Gynecol Scand. 2020;99(1):79-88.

4. Gensheimer M, Jones C, Graves C, Merchant NB, Lockhart AC. Administration of oxaliplatin to a pregnant woman with rectal cancer. Cancer Chemother Pharmacol. 2009;63(2):371-3.

5. Selig BP, Furr JR, Huey RW, Moran C, Alluri VN, Medders GR, et al. Cancer chemotherapeutic agents as human teratogens. Birth Defects Res A Clin Mol Teratol. 2012;94(8):626-50.

6. Jeppesen JB, Østerlind K. Successful twin pregnancy outcome after in utero exposure to FOLFOX for metastatic colon cancer: A case report and review of the literature. Clin Colorectal Cancer. 2011;10(4):348-52.

7. Koren G, Carey N, Gagnon R, Maxwell C, Nulman I, Senikas V. Cancer chemotherapy and pregnancy. J Obstet Gynaecol Can. 2013;35:263-80.

8. National Toxicology Program. NTP Monograph: Development effects and pregnancy outcomes associated with cancer chemotherapy use during pregnancy. NTP Monogr. 2013;2:i-214.

9. Song Y, Liu Y, Lin M, Sheng B, Zhu X. Efficacy of neoadjuvant platinum-based chemotherapy during the second and third trimester of pregnancy in women with cervical cancer: An updated systematic review and meta-analysis. Drug Des Devel Ther. 2019;13:79-102.

10. Briggs GG, Freeman RK, Yaffe SJ. Drugs in pregnancy and lactation 8th edition: A reference guide to fetal and neonatal risk. Obstet Med. 2009;2(2):89.

11. Avastin (bevacizumab). Genentech, Inc. 2009. Accessed May 31, 2015.

12. Zaltrap (ziv-aflibercept). Sanofi-Aventis. 2012. Accessed August 17, 2015.

13. Stivarga (regorafenib). Bayer HealthCare Pharmaceuticals Inc. 2012. Accessed August 17, 2015.

14. Erbitux (cetuximab). Bristol-Myers Squibb Co. 2015. Accessed August 17, 2015.

15. Vectibix (panitumumab). Amgen Inc. 2015. Accessed August 17, 2015.

16. Amant F, Han SN, Gziri MM, Dekrem J, Calsteren KV. Chemotherapy during pregnancy. Curr Opin Oncol. 2012;24:580-6.

17. Friedman JM, Weber Schondorfer C. Antineoplastic drugs. In: Schaefer C, Peters PWJ, Miller RK, editors. Drugs during pregnancy and lactation: Treatment options and risk assessment. 3rd Ed. Amsterdam: Academic Press. 2015. p. 374-99.