

Treatment of Metastatic Colorectal Cancer in a Pregnant Woman with Lynch Syndrome- A Case Report

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Introduction

Colorectal carcinoma is the third most common cancer diagnosed in females in the United States [1]. It accounts for 8% of the new cancers diagnosed in women and an estimated 63,700 new cases of CRC expected in 2015. CRC diagnosed in pregnancy is not common with an incidence of 1 in 13,000 pregnancies [2-4]. Management of a pregnant woman with CRC is challenging due to various unknowns to guide the antineoplastic treatment decision. CRC cases during pregnancy and use of chemotherapy agents have reported in the past decade [5-12]. Reporting of management of such situations is helpful in assisting clinicians to further investigating the use of chemotherapy agents in pregnancy. We report an unusual, but the challenging case of 24-year-old pregnant women diagnosed with metastatic colon cancer as a consequence of lynch syndrome treated with FOLFOX chemo regimen with no apparent fetal harm.

A 24 years old lady G1P0, 16 weeks' pregnant female with the history of hypothyroidism and family history positive for colon cancer in paternal grandfather presented to the local hospital with sudden onset lower abdominal pain. Ultrasound of the abdomen showed L adnexal mass. She underwent laparoscopic exam with the presumptive diagnosis of ovarian torsion which showed significant mass obscuring the L ovary. The initial attempt was made to dissect the mass, but it got ruptured, spilling the contents into the peritoneal cavity. At the point, colorectal surgeon got involved who cleaned the peritoneum, took a biopsy from omentum, proximal and distal colon, performed colostomy with drain placement. At that point, the patient was transferred to our facility for a higher level of care due to the complexity of the case.

The patient admitted to high-risk obstetrics service. Regular fetal assessments performed with no signs of fetal distress. Outside pathology slides were requested and examined by the team of pathologists. We also discussed with the surgeon who performed the urgent surgery. Final pathology results showed low-grade adenocarcinoma of 2.5 cm proximal colon with grossly identified perforation (sample A), low-grade adenocarcinoma of 3 cm distal colon with grossly identified perforation (sample B) and metastatic omentum adenocarcinoma (sample C). The initial pathological staging was determined to be pT4a (m), pN0 (m) 7 nodes examined, 0 nodes involved pM1(omentum). Initial CEA was normal, and ultrasound abdomen and chest x-ray did not show distant metastasis. Molecular testing showed alteration in multiple microsatellite loci, consistent with the high degree of microsatellite instability (MSI-H). MLH 1 promoter methylation status was also assessed, revealing no significant methylation of MLH1 promoter region in either tumor or normal tissue. Sequencing of the gene encoding DNA mismatch repair proteins including MLH1, MSH2, MSH6 and PMS2 was performed, and a mutation in the MSH2 gene i.e. c.1068delA, identified

confirming the diagnosis of hereditary nonpolyposis colorectal cancer (lynch syndrome). KRAS mutation was also found to be positive.

After a thorough discussion with the patient explaining benefits verses potential side effects of the chemotherapy regimen mFOLFOX6 to the patient and her baby in utero and after birth, she chose to retain the pregnancy and proceed with the treatment. Appropriate time given for wound healing and FOLFOX regimen with 25% reduce dose i-e Oxaliplatin 65 mg/m², Leucovorin 300 mg/m², 5FU 300 mg/m² IV bolus followed by 5FU 1800 mg/m² CIVI for 46 hours every two weeks, was initiated at 22 weeks' gestation. She received a total of 4 cycles of chemotherapy with transient nausea and cold sensitivity of hands and feet. Regular monitoring of the fetus performed at high-risk OB clinic. One-week prior (i-e 35 gestational week) to her scheduled delivery date, the patient presented to the local hospital with two episodes of witnessed seizure and blurry vision. Her blood pressure was found to be elevated. She was infused with IV magnesium sulfate and immediately transferred to our facility. A diagnosis of eclampsia and HELLP syndrome made. Next day, labor was induced with a normal vaginal delivery of a baby girl weigh 1925 grams and Apgar score of four at 1 min, eight at 5 min and eight at 10 min.

Pt underwent scans after the delivery revealing two mesenteric implants measuring 4.1 cm and 4.3 cm and enlarged left ovary. It was decided to treat with aggressive regimen i-e FOLFOXIRI with Avastin in an attempt to potentially convert the metastatic disease into resectable implants. The patient received five cycles of the regimen with pegfilgrastim(Neulasta) support every two weeks with the following doses; 5FU 2400 mg/m² over 46 hours, Oxaliplatin 85 mg/m², Irinotecan 150 mg/m², Bevacizumab 5 mg/kg. After five cycles, four additional cycles were given without Avastin with the omission of Oxaliplatin in the 9th round due to neuropathy of the hands and feet. A pap smear also performed which showed low grade squamous intraepithelial lesion. Following a total of 13 cycles of chemotherapy (4 FOLFOX while pregnant, 5 FOLFOXIRI w/ Avastin, 4 FOLFOXIRI), the patient underwent cytoreductive surgery, total abdominal hysterectomy, bilateral salpingo-oophorectomy and heated intraperitoneal chemoperfusion(HIPEC), a procedure usually performed at the end of the surgery to remove unseen abdominal tumors. Post op imaging showed no signs of cancers. She is started on estradiol 0.5 mg tab daily to counter the effects of surgical menopause. She is regularly following in the clinic without treatment. She is planning to get married soon. Her daughter is 12 months old and has so far achieved normal developmental milestones.

Discussion

Recent Surveillance, Epidemiology, and End Results (SEER) database analysis from 1975 to 2010 found the CRC incidence rate has increased in patients age 20-49 with an approx. 2% annual increase in

patients with the same age group [13]. CRC in pregnancy is likely to become more common because of the current trend of delayed pregnancies in the 30s and 40s. Management of the CRC is challenging due to data limited to retrospective cases, less experience of clinicians with multiple agents used simultaneously, varying teratogenic potential and the pharmacokinetic changes happening in pregnancy. The most concerning period for congenital malformations from chemotherapy exposure is the first trimester [2,14-17] with risk ranging 10-12%, followed by 8% in the second trimester and 6% in the third trimester [2,15,18,19]. Because of potential adverse effects like myelosuppression, bleeding and death during delivery, chemotherapy is not recommended three weeks before the expected delivery or beyond 35 weeks of gestation [2,3,14,17,18,20,21]. The U.S Food and Drug Administration (FDA) has categorized the chemotherapy drugs based on their known or potential teratogenic risk to the fetus [22]. Because of the lack of human evidence of potential or perceived harm, CRC antineoplastics are listed as category C, and D. The FDA has initiated the transition from using these classes because of their simplicity and soon medication prescribing information will incorporate a more descriptive method for pregnancy, lactation and fertility methods. To date, however, these risk categories are still in place, and the clinicians should use these guidelines to consider limitations when to encounter such scenarios.

The fluoropyrimidines, 5-Fluorouracil (5-FU) and capecitabine are the primary antineoplastic agents for the treatment of CRC when used as a single agent or in combination with additional chemotherapy. They have small molecular weights especially 5-FU with negligible protein binding and capecitabine about 35% albumin binding. Most of the experience in using 5-FU came from treating breast cancer and according to the 2013 National Toxicology Program (NTP) monograph. Thirteen pregnant women received 5-FU in their first trimester, 4 cases (31%) reported with major malformations, only 2 of 161 (1.2%) cases occurred when received 5-FU in the second or third trimester [17]. The only congenital abnormality found was hypothyroidism [16] when 5-FU was given to the pregnant woman with CRC alone or in combination (with oxaliplatin or irinotecan) after the first trimester [5-12]. This difference is likely due to difference administration where bolus dosing is used with FAC in breast cancer patients, whereas 5-FU in CRC is given as both a bolus and continuous infusion. With the available data, 5-FU beyond the first trimester appears to present a little concern for congenital malformations. Literature regarding capecitabine use in pregnancy is limited and 5-FU should be utilized when needed. Moreover, to avoid significant adverse effects of 5-FU, consideration for dihydropyrimidine dehydrogenase testing should be considered before the administration.

Oxaliplatin, a third-generation platinum has used in locally advanced and metastatic CRC. Seven pregnancies received oxaliplatin [5-9,23,24] with five pregnancies in combination with a fluoropyrimidine and leucovorin (FOLFOX), after the first trimester (initiated 13-23 weeks' gestation) [5-9], have been described. In one infant hypothyroidism was reported [16], while two infants were described as small for gestational age (born at 31 and 36 weeks' gestation). Irinotecan, a topoisomerase 1 inhibitor is used in mCRC in combination with additional chemotherapy [10,11]. In both cases, it was combined with 5-FU and leucovorin and treatment was initiated after the first trimester (at 18 and 23 weeks' gestation). The authors reported healthy infants in both cases. Angiogenesis inhibitors like bevacizumab, ramucirumab and regorafenib are indicated in mCRC and has no experience using in the pregnant woman described in the literature. Inhibition and disruption of the primary regulators involved

in the complex placental vasculature which requires vasculogenesis and angiogenesis can produce pregnancy complications. Thalidomide, an immunomodulatory and antiangiogenic agent, used by pregnant women for morning sickness resulted in an estimated 10,000 children having severe limb malformations [25,26]. Agents with similar properties are concerning and should not be used in pregnancy. Cetuximab and Panitumumab are epidermal growth receptor (EGFR) monoclonal antibodies, chimeric and fully human, respectively. They are used for wild-type KRAS mCRC alone or in combination with chemotherapy. EGFR plays a role in placental development, endometrial function, and embryonic growth during early pregnancy. Both agents should be avoided in pregnancy given the important role of EGFR in the maintenance of pregnancy and fetal growth and no human exposure. Furthermore, both agents are known to cause hypomagnesemia which may directly affect the fetus.

There are no recommended guidelines or regimen considered to be safe in pregnancy given the overall toxic effects of the chemotherapeutic agents [27].

Clinical guidelines for the management of colon cancer in pregnancy is available, however most of the literature reviewed and hence the recommendations are based on case reports.

As recommended by NCCN guidelines, FOLFOX regimen use is recommended for patients with advanced or metastatic disease. The FOLFOX regime consists of oxaliplatin, leucovorin and 5-FU. Use of oxaliplatin and 5-FU during pregnancy is considered as class D by the U.S. Food and Drug.

Use of 5- FU for colon cancer in pregnancy

For stage 3 tumors, adjuvant use of 5- FU is suggested [28] Use of 5-FU is highly teratogenic in animal models given the higher doses of chemotherapy used. 5-FU use was reported in the first trimester in one study. They reported 1 case of spontaneous miscarriage and 6 cases of IUGR out of 53 cases [29] the rest of the outcomes were all reported as normal. Another study reported second and third trimester use of 5-FU with cyclophosphamide and methotrexate. There were 12 cases reported with all pregnancies resulting in normal outcomes [30]. There was another study with 18 patients reporting normal outcomes in all cases being treated for breast and colon cancer in second and third trimester with 5-FU [31]. Several case reports have reported normal outcomes with the pregnancies as well as fetal loss when 5-FU has been used in first trimester of the pregnancy [32-36].

However, when intravenous 5-FU was used in second and third trimesters in combination with doxorubicin, cyclophosphamide and other chemotherapeutic agents for the treatment of breast cancer no clinically significant adverse effects were reported among 40 infants observed.

Among the available antimetabolites, when used in second and third trimesters, use of 5-FU has not been reported to be associated with increased risk of teratogenicity.

Use of FOLFOX for colon cancer in pregnancy

3 case studies reported the use of FOLFOX regimen from the gestational age of 13 weeks to 24 weeks for the treatment of colorectal cancer during pregnancy with positive fetal outcomes is all the cases. The babies were also followed until 3.5 years if age and all were found to be within normal limits for height, weight and neurological development [6-8].

Conclusion

Treating cancer in pregnancy with optimal anti-cancer regimen without harming the developing fetus is very challenging. For the best chances of survival of both the mother and the fetus, chemotherapy should not be delayed or postponed until the end of the duration of the pregnancy. Treatment decision should be made after proper patient and family counseling. Available evidence supporting the use of FOLFOX chemotherapy for the treatment of CRC from the second term onwards. The data is limited but shows relatively no to minor effects on mother and fetus. Long term follow-up of the infants in later childhood and adolescence is needed regarding cognitive dysfunction through reporting. CRC monoclonal antibodies and multikinase inhibitors should be avoided in pregnancy due to concerns regarding their mechanism of action and lack of human evidence. Our case report will further add the experience of FOLFOX chemotherapy use in the pregnant woman, to provide future guidance to make sound decisions by the other physicians.

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