Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/zmv9pm80

FOLFOX AND FOLFIRI CHEMOTHERAPY IN A METASTATIC COLORECTAL CANCER PATIENT: A CASE REPORT OF DUAL REGIMEN INTOLERANCE

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Abstract

Background: FOLFOX and FOLFIRI are standard chemotherapy regimens for metastatic colorectal cancer (mCRC). While both regimens are associated with distinct toxicity profiles, intolerance to both is uncommon and poses a major therapeutic challenge.

Case Presentation: The case of a 54-year-old male diagnosed with metastatic adenocarcinoma of the rectosigmoid region (stage IV B), confirmed to be microsatellite stable (MSS) on immunohistochemistry. The patient initially received 12 cycles of FOLFOX plus bevacizumab, achieving a partial metabolic response. Maintenance capecitabine was initiated but discontinued due to gastrointestinal intolerance. A subsequent whole-body PET-CT showed progressive disease. The patient was started on FOLFIRI with bevacizumab but developed severe grade 4 lower gastrointestinal toxicity and acute cholinergic syndrome, necessitating hospitalization and FOLFIRI regimen discontinuation. A rechallenge with the FOLFOX regimen was attempted; however, the patient again experienced significant intolerance. In view of prior fluoropyrimidine response, low-dose capecitabine was re-initiated with supportive care and close monitoring.

Conclusion: This case highlights the complexity of managing mCRC in patients who exhibit intolerance to both FOLFOX and FOLFIRI regimens. Early recognition of severe toxicity, careful dose modification, and personalized therapeutic planning are essential.

Keywords: Colorectal cancer, Chemotherapy, FOLFOX rechallenge, FOLFIRI toxicity, Capecitabine, Irinotecan, Palliative Care

Introduction

FOLFIRI is a chemotherapeutic combination of folinic acid (leucovorin), 5-fluorouracil (5-FU), and irinotecan. Irinotecan is a topoisomerase I inhibitor and is used in the treatment of cancers like colorectal cancer, pancreatic cancer, and lung cancer. Irinotecan is a prodrug that is metabolized in the liver to produce the active metabolite 7-ethyl-10-hydroxycamptothecin (SN-38) by carboxylesterase, a potent active metabolite that also inhibits topoisomerase I.[1] There are particular adverse effects seen with the irinotecan due to inhibition of acetylcholinesterase, leading to cholinergic symptoms like profuse sweating, salivation, bradycardia, miosis, abdominal cramping pain, diarrhea, increased lacrimation, nausea, and nasal discharge. FOLFOX is a combination of folinic acid (leucovorin), 5-fluorouracil (5-FU), and oxaliplatin which is used for colorectal cancer.[2] Oxaliplatin exerts cytotoxicity by inhibition of DNA replication and transcription. Among FOLFOX regimens, the symptoms of nausea and vomiting are mainly due to oxaliplatin, which is emetogenic.[3] The patient may experience nausea, retching, or emesis. Antiemetic prophylaxis is routinely recommended for chemotherapy induced nausea and vomiting.

Case Presentation

A 54-year-old male patient was diagnosed with a carcinoma rectosigmoid of the upper 1/3rd of the rectum. On biopsy, it showed adenocarcinoma and was characterized as stage IVB. Colonoscopy showed growth in the upper rectum at 10 cm from the anal verge, extending up to 14 cm and involving one-third of the luminal circumference. The scope was advanced up to the caecum, and the proximal mucosa appeared normal. Upper GI endoscopy showed a few erosions in the proximal duodenal (D1), while the second part of the duodenum (D2) appeared normal. Whole body PET-CT showed FDG-avid eccentric wall thickening (SUV max 7.1) over a 4.3 cm segment of the rectosigmoid and upper rectum, with perilesional stranding. FDG-avid nodes were seen in right cervical level V, supraclavicular, paratracheal, and subcarinal regions (largest 1.6 × 1.5 cm, SUV max 5). Multiple FDG-avid necrotic lesions (SUV max 4.2) were noted in both liver lobes, suggestive of metastases. Rectal biopsy showed poorly differentiated carcinoma, morphologically an adenocarcinoma. Immunohistochemistry (IHC) was done for mismatch repair protein expression to assess microsatellite instability status and possible Lynch syndrome. IHC showed microsatellite stability with intact expression of MLH1, MSH2, MSH6, and PMS2 — indicating proficient mismatch repair (pMMR) and a microsatellite stable (MSS) tumor. Cytokeratin 20 (CK20) positivity supporting the diagnosis of colorectal origin of the tumor. 2D-ECHO showed Grade-I LV dysfunction with EF 56%. Patient was a known case of diabetes since one month. Patient had mixed diet, tobacco user since 20 years, non-smoker, no similar family history, complaint of diarrhoea associated with rectal bleeding, and bladder movement were regular.

The patient was initially planned for palliative care and was administered the FOLFOX regimen of chemotherapy. The patient body surface area (BSA) was 1.57 m^2 and chemotherapy dose was calculated according to it. On Day 1, the patient received injection oxaliplatin at a rounded dose of 150 mg (from a calculated 157 mg), injection leucovorin 600 mg (rounded from 628 mg), and an injection 5-FU bolus of 600 mg (rounded from 628 mg). This was followed by a continuous infusion of 5-FU totaling 3500 mg over Day 1 and Day 2 (rounded from 3768 mg). Bevacizumab was administered at a dose of 10 mg/kg IV every 2 weeks with the biweekly FOLFOX regimen. The patient tolerated the treatment with FOLFOX regimen. After 11 cycles of FOLFOX with bevacizumab, PET CT revealed a partial metabolic response, and the patient was planned to start oral capecitabine as maintenance therapy after the 12th FOLFOX cycle.

The patient was started on maintenance capecitabine following initial response to first-line chemotherapy. However, after the first cycle, the patient developed abdominal pain and generalized weakness, leading to temporary discontinuation of the drug. A second cycle was cautiously attempted, but the patient again experienced significant abdominal discomfort, which was managed symptomatically. A whole-body FDG PET-CT was performed, which revealed disease progression, including increased FDG uptake and wall thickening involving the upper rectum, along with newly enlarged FDG-avid aortocaval, precardiac, and abdominosplenic lymph nodes.

Given the combination of clinical intolerance to capecitabine and radiological evidence of progression, the patient was transitioned to second-line therapy with FOLFIRI plus bevacizumab.[4] The patient's body surface area (BSA) was calculated at 1.49 m^2, and chemotherapy was initiated at reduced doses, with plans to escalate if tolerated. On Day 1, the patient received irinotecan at 200 mg (calculated dose 268.2 mg), leucovorin 500 mg (calculated 596 mg), and a 5-FU bolus of 250 mg (calculated 298 mg), followed by a continuous 5-FU infusion of 3000 mg over 46 hours (calculated 3576 mg). The dose reduction was due to prior adverse effects, with close monitoring planned to assess tolerance and guide potential dose escalation in subsequent cycles.[5]

Following initiation of the FOLFIRI plus bevacizumab regimen, the patient developed severe diarrhea, persistent vomiting, hypotension, and intense abdominal pain, consistent with grade 4 lower gastrointestinal (GI) toxicity as per CTCAE criteria.The patient was diagnosed with irinotecan-induced acute cholinergic syndrome (ACS), therefore, the FOLFIRI regimen was discontinued. The patient was admitted under internal medicine for conservative management, including IV fluids, antiemetics, and supportive care. After stabilization, the patient was reviewed in the oncology outpatient department, and a decision was made to rechallenge with the FOLFOX regimen, given prior better tolerability.
The rechallenge regimen included oxaliplatin 150 mg, leucovorin 600 mg, 5-FU bolus 600 mg, followed by 5-FU continuous infusion 3500 mg over 46 hours. However, shortly after administration, the patient experienced nausea, vomiting, and poor tolerance, leading to early discontinuation of the FOLFOX regimen as well. Due to intolerance to both FOLFIRI and rechallenged FOLFOX, further treatment options were considered with a focus on symptom control and quality of life. The infusion was stopped and the patient was managed conservatively for symptoms. In view of limited treatment tolerance and prior response to fluoropyrimidines, the patient was re-initiated on capecitabine at a cautious dose, despite earlier intolerance. Supportive measures were prescribed, including antiemetics, dietary counselling, and hydration advice. The patient was clinically stable at discharge and was advised close monitoring on an outpatient basis for adverse effects and tolerance to therapy. Based on WHO-UMC criteria, adverse reactions to capecitabine (GI toxicity), irinotecan (acute cholinergic syndrome), and oxaliplatin (nausea/vomiting) were all assessed as “probable”, given the clear temporal relationship, symptom resolution on dechallenge, and known drug profiles. The ADR was duly reported to PvPI (Pharmacovigilance Programme of India) through VigiFlow.

Discussion

This case highlights the rare and clinically significant challenge of dual-regimen intolerance in a patient with metastatic colorectal cancer (mCRC), specifically to both FOLFOX and FOLFIRI, which are mainstay for first- and second-line treatments. While each regimen is commonly associated with distinct toxicities—oxaliplatin-induced neuropathy and gastrointestinal intolerance in FOLFOX, and irinotecan-induced diarrhea and cholinergic syndrome in FOLFIRI—simultaneous intolerance to both regimens remains uncommon and limits therapeutic flexibility in advanced disease. The incidence of Acute Cholinergic Syndrome (ACS) with irinotecan has been reported to vary across studies but generally ranges between 30% to 50% of patients receiving irinotecan-based chemotherapy [6]. The incidence of grade 3/ 4 diarrhea is approximately 10% with FOLFIRI and 5% with patients receiving the FOLFOX regimen. Severe diarrhea requiring hospitalization has been reported with both regimens.

Both chemotherapy regimens can be associated with significant toxicities that can be managed by dose reductions or discontinuation.[7,8]

The patient initially responded well to FOLFOX plus bevacizumab, achieving a partial metabolic response, which aligns with existing data demonstrating improved survival outcomes when biologics are added to cytotoxic chemotherapy. However, intolerance to maintenance capecitabine, followed by grade 4 lower GI toxicity upon FOLFIRI initiation (likely due to irinotecan-induced acute cholinergic syndrome), reflects a hypersensitive phenotype to fluoropyrimidine- and irinotecan-based therapies. This suggests a possible pharmacogenetic predisposition, such as reduced UGT1A1 enzyme activity, although genetic testing was not pursued in this case due to resource limitations.[9]

Chemotherapy-related toxicities are a leading cause of treatment discontinuation and significantly impact prognosis in mCRC. In this patient, early onset of cholinergic symptoms, including diarrhea, abdominal cramping, and hypotension, are characteristic of acute irinotecan toxicity, which is mediated by acetylcholinesterase inhibition by the parent compound. Despite prophylactic dose reductions, intolerance persisted, reinforcing the unpredictable nature of severe ADRs in certain individuals.

A rechallenge with FOLFOX was attempted based on prior tolerability, but the patient again exhibited poor GI tolerance. Given cumulative toxicity and intolerance to both cytotoxic regimens, treatment options became limited. In such situations, clinical decisions must balance disease control with quality of life, emphasizing the importance of individualized treatment strategies. This case reinforces the growing need for biomarker-driven and tolerance-guided therapy. In patients with MSS/pMMR tumors, as seen here, immunotherapy remains ineffective, and chemotherapy remains the mainstay. Unfortunately, lack of actionable mutations (e.g., RAS/BRAF wild-type, HER2 negative, MSS status) in this patient precluded targeted therapies. Novel third-line options such as regorafenib or trifluridine-tipiracil (TAS-102) could be considered; however, the patient's prior intolerance to oral agents raised concerns for adherence and further toxicity.[10,11]

Re-initiation of low-dose capecitabine with close monitoring was a pragmatic decision, especially given prior disease response. This aligns with real-world practices where treatment de-escalation may be necessary to preserve patient function and palliate symptoms. Importantly, the role of supportive care—including hydration, nutritional counselling, and early symptom management—was crucial in maintaining outpatient stability.

Conclusion

This case highlights the difficulty of treating metastatic colorectal cancer when standard chemotherapy is not tolerated. Genetic testing, such as UGT1A1 for irinotecan toxicity and DPYD for fluoropyrimidine metabolism, can guide safer use of available drugs.[12] Testing for KRAS/NRAS, BRAF mutations and microsatellite instability helps in selecting targeted or immunotherapy options. Where no targeted therapy is possible, careful dose adjustment and supportive care remain important. Combining genetic information with clinical judgment offers the best chance of providing effective and safer treatment in such patients.

Conflict of interest None

Funding None

Availability of data and materials

All the data used and or analyzed during case report development have been included in the case presentation.

Consent

Written informed consent for publication of this case report was obtained from patient.

Acknowledgements
We would like to acknowledge the contribution of Dr Riya Mittal and Dr Jaanvi Sana Chhabra assistance during the course of this case.

Abbreviations
ACS – Acute Cholinergic Syndrome, ADR – Adverse Drug Reaction, BSA – Body Surface Area, CK20 – Cytokeratin 20, CTCAE – Common Terminology Criteria for Adverse Events, EF – Ejection Fraction, FDG – Fluorodeoxyglucose, FOLFIRI – Folinic Acid + 5-Fluorouracil + Irinotecan, FOLFOX – Folinic Acid + 5-Fluorouracil + Oxaliplatin, 5-FU – 5-Fluorouracil, GI – Gastrointestinal, IHC – Immunohistochemistry, IV – Intravenous, mCRC – Metastatic Colorectal Cancer, MSS – Microsatellite Stable, pMMR – Proficient Mismatch Repair, RAS – Rat Sarcoma Oncogene, BRAF – v-Raf Murine Sarcoma Viral Oncogene Homolog B, TAS-102 – Trifluridine/Tipiracil, UGT1A1 – Uridine Diphosphate Glucuronosyltransferase 1A1, UGIE – Upper Gastrointestinal Endoscopy, SUV – Standardized Uptake Value

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