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RESEARCH ARTICLE

CAPECITABINE INDUCED NECROTIZING ENTEROCOLITIS.

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Abstract

Introduction:-

Capecitabine is an antineoplastic agent belonging to pyrimidine antagonist which is used in the treatment of metastatic colorectal cancer. It is an orally active prodrug of 5-Fluorouracil (5- FU). After absorption it is converted into deoxy-5-fluoridine in the liver and is released into blood. Taken up by cells, it is hydrolyzed to 5-FU by thymidine phosphorylase. 5-FU is metabolized by dihydropyrimidine dehydrogenase(DPD).Since many breast and colorectal cancer cells express large quantity of this enzyme, they generate more 5-FU and suffer higher toxicity than normal cells. A combined regimen of capecitabine and oxaliplatin is frequently used in metastatic colorectal cancer[1]. Capecitabine is registered for treatment of patients following surgery of stage III colon cancer in the adjuvant setting, for treatment of metastatic colorectal cancer, first-line treatment of advanced gastric cancer and for treatment of locally advanced or metastatic breast cancer (European Medicines Agency (EMEA), 2015)[2]. Here we report a case of necrotizing enterocolitis secondary to the use of capecitabine in the treatment of carcinoma stomach stage III and discuss its relevant pathophysiology, clinical presentation and management.

Our aim is to create an awareness regarding capecitabine induced necrotizing enterocolitis which is a rare and life threatening adverse event.

Case report:

A 65years old male was evaluated for abdominal pain, vomiting and loss of appetite. The patient's past medical history shows that he is a known case of COPD and is on inhalers. He is also positive for HbsAG test. Ultrasonography(USG) abdomen done showed suspicious pyloric wall thickening. Oesophago-gastro-duodenoscopy (OGD scopy) done showed growth incisura. Biopsy reports showed poorly differentiated adenocarcinoma stomach. He underwent distal gastrectomy, D2 dissection and esophago jejunostomy. Histopathology reported as tumor size of 8 x 5 x 2 cm, grade III, poorly cohesive carcinoma, margins free and 14/22 lymph nodes positive. He came to hospital for further evaluation and management and was planned for adjuvant chemotherapy with oxaliplatin and capecitabine (capeOX) regimen. The patient successfully tolerated first three cycles of chemotherapy. But post fourth cycle of capecitabine, patient presented with complaints of loose stools and abdominal pain.

Diagnosis:

Clinical examination showed that the patient's ECOG performance status as 1. The patient was afebrile and vital signs were normal. Post 4th cycle the patient presented with complaints of giddiness, loose stools and abdominal pain. On clinical examination abdomen was distended and tenderness was positive. USG was done and it showed that the patient got diagnosed with Necrotising enterocolitis. This diagnosis was further confirmed by a CT scan. Blood investigations revealed that the patient have hypokalemia.

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Discussion:-

Capecitabine is a systemic prodrug of 5-FU which is FDA approved for the use in adjuvant therapy of colorectal and gastric cancer, first line therapy in metastatic colorectal cancer and metastatic breast cancer. Capecitabine when compared to 5-FU have the added advantage of oral administration making it expedient in home based setting, thereby minimizing need for venous access as well as hospital stay.[3]

Capecitabine releases 5-FU for extended durations delivering higher drug concentrations at tumour sites which likely causes a range of GI side effects. These include nausea, vomiting, mucositis, diarrhea, GI hemorrhage, necrotizing enterocolitis and toxic dilatation of the intestine. The incidence of diarrhea has been reported to be 47-67% and is graded 1-4 depending on severity[4]. Capecitabine seems to be eligible for the treatment of advanced breast and colorectal cancer. A review study compared capecitabine and 5-FU showed that the former have superior effectiveness with a statistically significant difference.[5]

Necrotizing enterocolitis is a medical condition where a portion of bowel dies. Necrotizing enterocolitis is also known as neutropenic enterocolitis or agranulocytic enterocolitis. This is observed mainly in DPD deficient patients.[6] capecitabine have a rare adverse drug reaction of necrotizing enterocolitis. Studies show that the symptoms of this adverse effect is seen during the third week of chemotherapy.[7]

Management:

He was initiated on symptomatic management with IV antibiotics Meropenem 1g TID and Metrogyl 400mg TID, probiotics, syp.Potclor 10ml TID for pottasium correction and other supportive medications. Poor prognosis of this situation was discussed in detail with the patient relatives. He was given supportive management in the form of Nor adrenaline, blood component transfusions and other supportive medications. Following which he clinically improved and stool passed. However he developed abdominal distension, sluggish bowel sounds and abdominal discomfort and was continued with symptomatic management. In view of significant financial constraints, his relatives opted to continue further supportive care at nearby hospital. Hence he is being discharged at request.

The European Society of Medical oncology(ESMO) suggest that the initial treatment should be a broad spectrum antibiotic which may cover enteric gram negative organisms, gram positive organism and anaerobes. Reasonable initial choices include monotherapy with piperacillin-tazobactam or imipenem-cilastatin or combination therapy with cefepime or ceftazidime along with metrinidazole .[8]

Conclusion:-

Evidences supports that capecitabine is a useful agent in adjuvant and advanced colorectal cancer treatment. Experiences suggest that its use should be tempered with vigilance for serious gastro-intestinal morbidity.[8] Early detection by health professionals and awareness regarding the predictable adverse effects related to the use of this drug can help in minimizing the adverse effect.

So as to overcome or prevent this situation, the physician should provide adequate information regarding the potential adverse effect of this drug provided the physician should also recognize the early symptoms of the ADR. This can go a long way to prevent or minimize predictable adverse drug effects of these chemodrugs.[9]

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