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Gastrointestinal related symptoms on FOLFIRI regimens in resectable stage III colorectal cancer patients: A retrospective study

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Abstract

Introduction: Irinotecan is a second-line chemotherapy for colorectal carcinoma. The most frequent irinotecan toxicity is severe diarrhea and suppression of the immune system (neutropenia). Other side effects include nausea, hyperbilirubinemia, fatigue, emesis, fever, weight loss, alopecia, edema, dyspnoea and thromboembolism. Gastrointestinal related symptoms were the most common side effect following this chemotherapy regimen.

Methods: This is a retrospective study which evaluated 10 patients with resectable stage III colorectal adeno carcinoma from January till December 2017, whose given adjuvant chemotherapy with FOLFIRI regimens. Data were taken from medical records during chemotherapy period for six months. Any gastrointestinal related symptoms during this period would be reported as Irrinotecan related side effects, and patients that could not completed the chemotherapy cycle will be excluded.

Results: There were 10 patients included in this study, consisting of 6 male and 4 women. Patients age ranged from 32 to 65 years with an average of 51.6 years. Of the total patients, 5 patients had left sided colon adeno carcinoma, 3 patients with rectal carcinoma, 1 patient with sigmoid colon adenocarcinoma, and 1 patient with caecum carcinoma. All of the patients had post-chemotherapy complaints, such as nausea, vomiting, and diarrhea which could be tolerated well conservatively. 2 patients were excluded during this period because the symptoms can not be tolerated well and chemotherapy was interrupted.

Conclusion: Gastrointestinal related symptoms following FOLFIRI chemotherapy were common, the routine use as chemotherapy regimen should be evaluated later.

Keywords: FOLFIRI regimens, gastrointestinal symptoms, colorectal cancer

Introduction

Since the middle of the previous century, 5-fluorouracil (5-FU) has become an option in the treatment of colorectal carcinoma. The initial addition of folinic acid (leucovorin) and the addition of oxaliplatin (OX) further result in better response rates, longer remissions and improved survival of patients. Furthermore, the combination of folinic acid, 5-fluorouracil, and oxaliplatin, ie, the FOLFOX regimen, becomes a well-developed treatment for colorectal malignancies either as monotherapy or as an adjuvant for surgery ^[1].

Results of the International Study of Multicenter oxaliplatin / 5-fluorouracil / leucovorin in the adjuvant treatment of colon carcinoma (MOSAIC) in 2004, together with the National Surgical Adjuvant Breast and Bowel Project (NSABP) C -07 report in 2007, revealed that adding oxaliplatin to the fluorouracil regimen (FU) combined with leucovorin (LV) which results in a significant, 3-year free condition. FOLFOX boosts mood in MOSAIC trials. Following this finding, 12 cycles of FOLFOX [folinic acid (leucovorin), fluorouracil, and oxaliplatin] became the standard adjuvant regimen for the treatment of stage III colon carcinoma ^[2].

Irinotecan is second-line chemotherapy for advanced-stage colorectal carcinoma (KKR) following the failure of first-line chemotherapy with oxaliplatin and 5-fluorouracil. Irinotecan is activated by hydrolysis to SN-38, a topoisomerase inhibitor I. It is then inactivated by glucuronidation by uridine diphosphate glucuronosyltransferase 1A1. Inhibition of topoisomerase I by SN-38 active metabolites ultimately leads to inhibition of both replication and DNA transcription. Unlike hepatocytes, other cells in the body have no way of detoxifying SN-38 through glucuronidation, thus contributing to high cytotoxicity. The most frequent irinotecan toxicity is severe diarrhea and suppression of the immune system (neutropenia). Other side effects include nausea, hyperbilirubinemia, fatigue, emesis, fever, weight loss, alopecia, edema, dyspnoea, and thromboembolism ^[1,3].

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Methods

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Results

There were 10 patients consisting of 6 male and 4 women. Patients age ranged from 32 to 65 years with an average of 51.6 years. Of the total patients, 5 patients had left sided colon adeno carcinoma, 3 patients with rectal carcinoma, 1 patient with sigmoid colon adenocarcinoma, and 1 patient with caecum carcinoma. All of the patients had post-chemotherapy symptoms, such as nausea, vomiting, and diarrhea.

Table 1: Patients Characteristic

Characteristic	n
Tumor site	
Caecum – Ascending Colon	1
Transverse Colon	-
Descending Colon	5
Sigmoid Colon	1
Rectal	3
Symptoms	
Nausea	5
Vomite	2
Diarrhea	3

Discussion

Intestinal mucositis (IM) is a common side effect of irinotecan-based chemotherapy. The involvement of inflammatory mediators, such as TNF- α , IL1- β , IL-18 and IL-33, has been demonstrated. However, the role of adaptive immune system cells, whose activation is partially regulated by these cytokines, is yet unknown [4, 5, 6].

The role of regulatory T cells (Tregs) in irinotecan-induced IM are important in the control of intestinal damage induced by irinotecan, and their depletion showed a deleterious effect on IM. Activation of these cells appears to be a compensatory mechanism for intestinal inflammation [7].

The widely applied cytotoxic agent irinotecan (CPT-11) as a representative agent and demonstrates that treatment induces massive release of double-strand DNA from the intestine that accounts for the dose-limiting intestinal toxicity of the compound. Specifically, "self-DNA" released through exosome secretion enters the cytosol of innate immune cells and activates the AIM2 (absent in melanoma 2) inflammasome. This leads to mature IL-1 β and IL-18 secretion and induces intestinal mucositis and late-onset diarrhea [4, 6, 7].

Gastrointestinal syndrome is a well-recognized side effect associated with a variety of chemotherapeutic agents, particularly irinotecan (CPT-11) and fluorouracil (5FU). As the first-line treatment for colorectal cancer (CRC), the clinical benefit of CPT-11 is limited by its adverse effect of severe diarrhoea, which occurs in ~ 40% of patients receiving CPT-11 treatment. Persistent or severe diarrhoea is not only a life-threatening side effect for CRC patients, but also can influence efficiency of chemotherapy through a need to reduce treatment doses or discontinue therapy. Thus far, the mechanism of CPT-11-triggered life-threatening gastrointestinal syndrome is poorly

understood. Clinical management of diarrhoea reflects the need for recognition of the early warning signs and the need for early and aggressive management. Of note, several lines of evidence suggest that CPT-11-triggered diarrhoea is associated with the production of the pro-inflammatory cytokines IL-1 β and IL-18 suggesting an immunogenic response. Previous studies have also demonstrated an anticancer effect of CPT-11-associated anti-tumour immunity [3, 4, 6].

Conclusion

Gastrointestinal related symptoms following adjuvant chemotherapy on stage III colorectal adeno carcinoma were more common in FOLFIRI regiment, we must reevaluated about the routine use of this regiment including the side effect management.

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