

STUDY BASED ON ADVERSE DRUG REACTIONS ASSOCIATED WITH FLUOROURACIL (5-FU) CALCIUM-FOLINATE THERAPY IN PATIENTS SUFFERING FROM COLORECTAL CANCER.

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Abstract:

Introduction: Fluorouracil (5-Fu) is one of the effective chemotherapeutic agents especially used to treat solid tumours including breast cancer and digestive tract cancers. **Objective:** objective of the study is to assess the response of the patients with regard to adverse drug reactions (ADRs). **Design:** A prospective observational study. **Place of study:** Cancer Hospital Jamshoro Pakistan. **Duration of study:** May 2015 to December 2017. **Methodology:** This study included 160 patients both male and female aged above 18 years suffering from colorectal cancer and receiving Mayo regimen (Fluorouracil(5-Fu) 370-426 mg/m² and calcium folinate is given 20 mg/m² in day 1-5) by purposive sampling technique and data collected by interviewing patients and recording data in a questionnaire, which than compared with British National Formulary (BNF) and Hartwig and Siegel scale to assess the severity of every response. **Results:** Present study identified various ADRs with the frequency of occurrence and severity receiving mayo regimen for treatment of colorectal cancer. Patients showed various responses among which most common were fatigue, nausea and emesis, anemia, acidity and alopecia. High severity ADRs that is of level 3 of severity scale was reported especially by those of old age and females and these can be easily prevented and controlled with the help of supportive therapies. **Conclusion:** The study reveals that 5-Fu and calcium folinate combination therapy is associated with various ADRs and majority of the patients have shown a response towards the therapy that is manageable. Therefore, only those proved to be most vulnerable should be given additional care to ensure safety during the therapy.

Keywords: ADRs, 5 FU therapy, Colorectal Cancer, Mayo regimen.

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Introduction:

Colorectal cancer is one of the frequently occurred among male and female and ranked as 3rd most lethal cancer even in developed countries and 50% of patients develops metastasis leading cause of death in west^{1,2,3,4}.

Colorectal cancer is type of cancer which originates in colon or rectum. Its synonyms include colon cancer and rectal cancer but due to similar features they are merged and hence referred as colorectal cancer. Usually male are affected more than females in both developing and western countries but rectal cancer is more common in underdeveloped countries than western. In Pakistan, older as well as young

population incidence rate is increasing by the passage of time. Symptoms of colorectal cancer include altered bowel habits, appearance of blood in faeces, discomfort in abdomen & weight loss. In metastatic disease symptoms depends upon the organ affected such as liver metastasis cause jaundice, abdominal pain, lungs include chest pain, dyspnoea etc^{5,6,7}

Factors which contribute towards the developing colorectal cancers include: Hereditary tendency, aging, obesity, reduced physical activity, dietary component especially red meat (beef, lamb), processed food material especially meat, using high temperature for cooking which generate toxic components, smoking and heavy use of

alcohol are the common factors responsible for colorectal cancer⁵.

The treatment of colorectal cancer with 5-fluorouracil and calcium folinate therapy proved very efficient in treating even an advanced disease and increase in the survival rate of the patients up to a year or even more as reported by surveys. 5-Fu calcium folinate therapy not only efficient in terms of medicinal effects but also cost effective and safe treatment protocol^{8,4}

Fluorouracil (5-Fu) is one of the effective drug belonging to antimetabolite class of chemotherapeutic agents which act by inhibiting cancer cells division by combining with their genetic material especially used to treat solid tumors including breast cancer and digestive tract cancers. The common toxic symptoms include mucositis, bone marrow suppression^{9,10,11}.

Calcium Folate a folic acid metabolite use to enhance the effect of 5-fluorouracil improves the response rate but it does not affect the survival rate as reported by the survey and clinical studies^{12,13,10,14}.

Most common effective regimen is Mayo regimen in which 5-Fu 426 mg/m² and calcium folinate is given 20 mg/m² in day 1-5 repeated monthly or every fourth week. Various studies have shown that as response rate varied with different populations similarly adverse reaction response also varied. De Gramont et al, s study presented that the patient have shown critical response and most common effect found to be anemia account for 80% of patients but majority were with grade 1 toxicity and nausea in more than 50% of the patients¹⁵.

In contrast Douillard et al's study presented a patient response which were highly critical and ADRs were of highest frequency and intensity and most common effects found were anemia and neutropenia 87%, among all effects reported whereas diarrhoea 76% patients and emesis reported by 75% patients^{11,16}.

Methodology

An prospective observational study conducted include 160 patients suffering from colorectal cancer aged above 18 years on Mayo regimen 5-Fu 370-426 mg/m² and calcium folinate is given 20 mg/m² in day 1-5) by purposive sampling from Cancer Hospital Jamshoro Pakistan from May 2015 to December 2017, interviewed during follow up session with Prescriber after receiving at least one cycle of the combination therapy and their response recorded in questionnaire and verified through Standard reference BNF (British National Formulary) and severity of each response were compared against ADR severity scale (Hartwig and Siegel scale). Principles of Declaration of Helsinki were followed during the conduct of following research^{10,17}.

This study included all male and female patients receiving mayo regimen for the colorectal cancer aged above 18 years. All patients receiving other concomitant therapies for treating other severe diseases such as tuberculosis, HIV, hepatitis and

any other condition that could interfere with the accuracy of results.

Results:

The present study enrolled 160 patients including both male and female group suffering from colorectal cancer and receiving 5-Fu and calcium folinate combination therapy for its treatment at Cancer Hospital Jamshoro Pakistan. Majority of the patients were male and account for 55.625% (Table 1). Most frequent age group were between 40-60 years with mean age of 42.569 as present in Table 1. ADRs reported by the patients were recorded in a questionnaire and these were verified through British National formulary and Hartwig and Siegel scale (ADR severity scale)¹⁷.

All the patients showed multiple ADRs and of different severity level and those with severity level up to 2 and above according to Hartwig and Siegel scale were included in results, in which female patients and male patients aged equal to 60 years and above found to be more vulnerable towards these ADRs in frequency as well as from severity point of view which are represented in Table 2.

Most common ADR found were fatigue and 79 patients out of 160 were affected which persist for long duration after every dose cycle limiting mobility in especially vulnerable group of patients such as women and elderly male. Acidity arises as second most common ADR in colorectal patients and which also persist for more than 24 hours up to even 48 hours in few patients. and emesis also found to be one of common ADRs of the therapy and most common among gastrointestinal disturbances associated with the therapy and patients suffer from the symptoms for 1-3 days after every cycle. The vulnerable group occasionally requires an I/V (Intravenous) nutritional supplements to maintain normal health and avoid disturbances in the actual therapy schedule which can adversely affects the therapy goals. Alopecia also found to be one of the frequent ADRs among the patients of mayo regimen. The patients reported it as of less severity. Other gastrointestinal symptoms were reported by less number of patients and severity was. Similarly the heart problems were also reported by a minimum number of patients with profound discomfort while bone marrow suppression symptoms appeared more frequently with higher percentages such as anemia, leucopenia and thrombocytopenia and few patients required the I/V therapy to attain the normal blood cell count. Neither of the enrolled patients' record has showed that they had suffered from interruptions in therapy as a result of these blood disorders which is one of the factor that lead to extend the duration of therapy schedule and increases inconvenience in patients in terms of health and therapy expenses. All the high severity ADRs reported were usually of level 3 in Hartwig and siegel scale and these were effectively controlled with the help of supportive therapies, which showed that the this therapy is comparatively safe while treatment is being given.

Table.1. Gender and Age Distribution of Patients enrolled.

Variable		No of Patients	(%)
Gender	Male	89	55.625
	Female	71	44.375
	Total	160	100
Age Groups	18-40	66	41.25
	41-60	84	52.5
	>60	10	6.25
	Total	160	100

Table 2. ADRs observed in patients in a Mayo regimen (5-Fu 370-426 mg/m² calcium folinate 20 mg/m²/day)

Sr.no	ADRs	No of Patients	(%)
1	Nausea & Emesis	60	37.5
2	Dyspepsia	37	23.125
3	Loss of appetite	48	30
4	Acidity	62	38.75
5	Diarrhoea	43	26.875
6	Mouth sore	20	12.5
7	Racing heart	20	12.5
8	Fatigue	79	49.375
9	Restlessness	36	22.5
10	Giddiness	47	29.375
11	Numbness	10	6.25
12	Leukopenia	49	30.625
13	Thrombocytopenia	48	30
14	Anaemia	66	41.25
15	Alopecia	50	31.2

Discussions:

Various studies presenting variety of ADRs associated with 5- Fluorouracil and leucovorin combination which are severe. This study also identified numerous ADRs but severity found to be less as compared to these studies.

Fotheringham, et al presented a review in which they mentioned that 5-Fu based therapy is responsible for fatal toxicities which include severe diarrhea, cardiac problems and blood disorders and approximately 20% patients suffer from grade 3/4 toxicities. Present study found these ADRs with severity level 3 which were successfully managed with supportive medication¹³.

Pearce et al., 2017 conducted an observational cohort study in which 142 patients enrolled were suffering from colorectal cancer and found 46-65 years as most common age group, present study also found age group between 41-60 years as most affected group. Diarrhea, constipation, mucositis, vomiting, fatigue found to be most common undesirable effects with frequency of more than 50%. Frequencies of these ADRs were comparatively less in present study subjects¹⁸.

Khan et al., 2012 study reported that 5 fu and leucovorin cardio toxic symptoms appeared in 3(18.75%) patients out of 16 patients receiving the combination therapy, which in this study subjects was 12.5% suffering from racing heart¹⁹.

Findings of this study are comparable to the study of Degramont et al,(2000) clinical study which

presented that emesis was reported in 29.4% which in this study was 37.5%. Diarrhea was 50% in this study it was 26.875 %. Mouth sores was 35.6% in this study it was reported by least number of the patients with frequency of 12.5%. Alopecia 18.8% in their study whereas in this study it was appeared more frequently than them that is 31.25%. Among blood disorders anemia appeared more frequent the percentage was 81.4%, thrombocytopenia 29.4% in their study which in this was 41.25% and 30% respectively. Leukopenia was 30.2% similarly it was 30.625 % in this study. Their study results presented that the occurrence of low severity ADRs were more common as compared to high severity one. Similarly, in our study patients reported ADRs with low to a severity level and these were manageable²⁰.

On the other hand our study is inconsistent with the study presented by the Douillard et al (2002) presenting results with highest frequency as well as severity of the ADRs associated with the 5-Fu and calcium folinate therapy as compared to another regimen. The subjects of our study have shown ADRs which were less in frequency as well as intensity. The frequency of various ADRs presented in their study include Diarrhoea was 76%, mouth sores 75%. Nausea & emesis 75%, Leukopenia appeared with 66%, thrombocytopenia 31%, Anemia 87%¹¹.

Present data comparisons reveal that although patient response towards therapy is critical one and require effective care planning. Mayo regimen which is still in practice in developing countries like Pakistan can serve as clinically as well as cost effective therapy option. Its selection as therapy should not be dropped because of toxicity data based on result of international clinical reports till majority of the local patients also respond in critical way as presented by them.

Conclusion

The study reveals that 5 Fu and calcium folinate combination therapy is associated with various ADRs and majority of local patients have shown a severity level that can be managed with supportive therapy. Therefore patients must remain in constant check by health professional's especially vulnerable group to make the therapy most safe and effective by overcoming the associated ADRs.

ETHICS APPROVAL: The ERC gave ethical review approval

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

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