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THE SEVERITY OF 5-FLUOROURACIL INDUCED GASTROINTESTINAL (GI) MUCOSITIS IT'S IMPACT ON TREATMENT.

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ABSTRACT

This study attempts to throw some light on the severity of gastrointestinal mucositis among cancer patients on chemotherapy. Number of 120 cancer patients, who were on chemotherapy (5fluorouracil) attending Radiation and Isotope Center in Khartoum was enrolled. A questionnaire results showed the patients were developed diarrheal toxicity revealing that, most patients were in grade (1) 79.8%, while only about 9% of them were having, grade (2), grade (3) and grade (4) approximately had equal distribution representing 5.6%. Four patients developed oral mucositis had equal distribution representing 50% in grade1 and grade2.

KEYWORDS: severity, gastrointestinal mucositis, oral mucositis, cancer patients, 5fluorouracil

Rationale

That has mucositis as an adverse effect associated with 5FU used in treatment. Mucositis can be painful and, may lead to life threatening complications and that why it is important to study the severity of effects of this drug will be investigated throughout this study.

INTRODUCTION

Oral and gastrointestinal mucositis caused by high-dose chemotherapy and/or radiation continues to be an important clinical problem. Fortunately, there have been strategic advances over the past decade in understanding the molecular basis of the injury, providing opportunities for the development of drugs and devices to manage toxicity. The guidelines detailed below represent updates from the version published in the 2011 *Annals of Oncology*[1], which were primarily based on the previous version of the guidelines produced by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO).[2]

Mucositis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract.[1] Mucositis can occur anywhere along the gastrointestinal (GI) tract, but oral mucositis refers to the particular inflammation and ulceration that occurs in the mouth.

Immunodeficient patients frequently exhibit a condition on the oral mucosa which is clinically described as oral mucositis. This condition has no known microbial or viral vector that has been implicated as the causative agent. The immunodeficiency that preceded the appearance of mucositis may arise spontaneously from genetic factors, may be caused by infections, e.g., the HIV virus or mucositis be induced as a result of chemotherapy or radiation therapy for neoplastic diseases. This condition has been difficult to treat and has not responded to treatment with antimicrobial agents.

Grading and severity assessment of Mucositis

Oral mucositis

a variety of assessment scales exist for measurement of oral mucositis. Two of the most commonly utilized scales are the WHO and National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scales[2]: WHO scale for oral mucositis Grade 0 = No oral mucositis Grade 1 = Erythema and soreness Grade 2 = Ulcers, able to eat solids Grade 3 = Ulcers, requires liquid diet (due to mucositis)Grade4 = Ulcers, alimentation not possible (due to mucositis)NCI Common Terminology Criteria for Adverse Events (CTCAE)Grade 1 = Asymptomatic or mild symptoms; intervention not indicated. Grade2 = Moderate pain; not interfering with oral intake; modified diet indicated Grade 3= Severe pain; interfering with oral intake Grade 4 = Life-threatening consequences; urgent intervention indicated Grade 5=Death.[3]

Most of the scales that are utilized for clinical care incorporate the collective measurement of oral symptoms, signs and functional disturbances. In comparison, some scales are primarily ocentered in clinician-based observation of mucosal tissue injury (e.g. erythema, ulceration). These latter scales have particular value in clinical trial-based assessment of oral mucositis. [4] Gastrointestinal mucositis grading: Diarrhea grades: In contrast, there are a limited number of instruments available for assessment of gastrointestinal mucositis. Common Toxicity Criteria for diarrhea, adapted from the National Cancer Institute these scales typically measure indirect outcomes of mucosal injury, including diarrhea. However, interpretation of such data can be confounded by other clinical conditions and interventions that also contribute to the event being measured. New technologies may lead to enhanced assessment strategies for gastrointestinal mucositis. Tracheal mucositis, pharyngeal mucositis, laryngeal mucositis, small intestinal mucositis, rectal mucositis and anal mucositis are terms that can be scored separately in the CTCAEv4.03 within the system organ class 'Gastrointestinal disorders–Other, specify'. Diarrhea is a term that is scored frequently within gastrointestinal mucositis also, which should not be confused with loose stool. The Bristol stool chart[5] is a useful tool to help identify variation in consistency of stool. The stools are classified into seven types, with types 5 and 6 tending towards diarrhea but still loose stool and type 7 actually as diarrhea, since that is watery stool. Since according to the NCI-CTCAE definition only watery stool is diarrhea, this delineation between the two types is important. Furthermore, it is important to delineate this range of stool consistency in order to optimize clinical decision making for these patients. NCI-CTCAE version 4.03.[2]

Grade 1 = increase of <4 stools per day over baseline; mild increase in ostomy output compared with baseline

Grade 2 = increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared with baseline

Grade 3 = increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe output compared with baseline; limiting self-care increase in ostomy activities of daily living (ADL)

Grade 4 = life-threatening onsequences; urgent intervention indicated

Grade 5 = death

Aim

To assess the severity of 5-Fluorouracil Induced Gastrointestinal (GI) Mucositis by WHO grading among cancer patient received chemotherapy (5flurouracil).

METHOD AND MATERIAL

An observational case – finding hospital based study, the study was conducted at Radiation and Isotopes center-Khartoum (RICK). Cancer Patients who are on chemotherapy '5fluorouracil' and who attend the Radiation and Isotopes Centre Khartoum (RICK) hospital to take "5fluorouracil during study data collection period of time From (October to November 2014).

Statistical analysis

The data collected was tabulated and analyzed using manual calculator, Microsoft excel and SPSS statistical software version 16. Chi square was employed to assess the significance among variables. A p-value of <0.05 was considered to be significant.

RESULTS

After being properly revised the collected data were then classified, interpreted and presented in the following sequences:

Table#1: Demographic characteristics of studied patients (n: 120).

Demographic characteristics	Frequency (%)
Age Groups(Yrs.)	
15-30	18(15)
31-50	44(36.7)
51-70	45(37.5)
71-100	13(10.8)
Gender	
Male	58(48.3)
Female	62(51.7)
Educational level	
Illiterate	32(26.7)
primary school certificate	40(33.3)
secondary school certificate	31(25.8)
university graduate & above	17(14.2)
Occupation	
Health professional	3(2.5)
Teacher	8(6.7)
Labor	21(17.5)
House wife	52(43.3)
Others	36(30)

When they were classified according to tumor site 32 (26.9%) in Nasopharynx, 25 (21%) in Breast, 24 (20.2%) in esophagus, Stomach and Uterus approximately in equal distribution representing 12 (10.1%) and only 5(4.2%) in lung.

Distribution of the study sample according to duration since the diagnosis of disease, showed that 104 (86.7%) between 1-15 months, 13 (10.8%) 16-30 months and 3 (2.5%) 31-60 months.

Disease characteristics	Frequency (%)
Disease site	
esophagus	24 (20.2)
Nasopharynx	32 (26.9)
Lung	5 (4.2)
Stomach	12 (10.1)
Prostate	9 (7.6)
Breast	25 (21)
Uterus	12 (10.1)
Diagnosis duration(months)	
1-15	104 (86.7)
16-30	13 (10.8)
31-60	3 (2.5)

Table#3: Details of medicaments received by studied patients (n: 120): It was noticed patients on the 2nd cycle of chemotherapy were found to constitute 40(33.3%), where those on the 3rd cycle were 38(31.7%), 4th cycle 17(14.2%), 6th 13(10.8%), 5th 10(8.3%), 7th and 8th show same percentage 1(.8%). The study showed that 83(69.2%) of the study population have not received pervious chemotherapy while 37 patients (30.8%) received pervious chemotherapy. Out of the 62 patients (51.7%) receiving concurrent chemotherapy 48 (77.4%) patients were found to receive cisplatin while only 14 patients (22.6%) used carboplatin.

Treatment details	Frequency (%)
Current cycle	
2nd	40(33.3)
3rd	38(31.7)
4th	17(14.2)
5th	10(8.3)
6th	13(10.8)
7th	1(.8)
8th	1(.8)
Pervious chemotherapy	
Yes	37(30.8)
No	83(69.2)
Concurrent chemotherapy	

Yes No	62(51.7) 58(48.3)
Type of concurrent chemotherapy cisplatin carboplatin	 48(77.4) 14(22.6)
Total	120

Figure1; Most of the studied patients developed diarrheal toxicity revealing that most patients were in grade(1) 79.8%, while only about 9% of them were having grade (2), grade3 and grade 4 approximately had equal distribution representing 5.6%.

Figure2: This figure representation showed that the only 4 patients that developed oral mucositis had equal distribution representing 50% in grade1 and grade 2.

DISCUSSION

5Fu is an anti -metabolite that acts on the enzyme thymidylate synthetase which in turn block DNA synthesis; there by exerting its anti-tumor effects.[6] Recognized common toxicities from 5-FU therapy include diarrhea and myelosuppression fluorinated pyrimidine and gastrointestinal mucositis.

In this study is determination of the, severity of gastrointestinal mucositis among cancer patients receiving 5fluorouracil was checked by using questionnaire, 120 subjects (patients) with cancer and who were on 5fluorouracil attending the Radiation and Isotopes Center during of specified period of time, The Results assembled from this study will also be compared with results obtained from previous researches, as a check for both studies. As previously observed from the results of the study, most of participants were attended the RICK(Radiation and Isotopes Center of Khartoum), were fall in age group 51-70 years representing 37.5% (45 patients), whereas the least common age group were 71-100 years representing only 10.8%.

However, in this study the males and females were almost equal in numbers percentage Most of patients were married 103(85.8%).

Classification of the study according to patient education, most of them were having primary school certificate 40 (33.3%) and Illiterate 32(26.7), followed by secondary school certificate 31(25.8).

Out of total 120 patients 52(43.3%) House wives, 21(17.5%) Laborers, 36(30%) others (farmers, policeman, engineers and beakers), 8(6.7%) Teachers and 3(2.5%) Health professional.

According to tumor site 32 (26.9%) in Nasopharynx, 25 (21%) in Breast, 24 (20.2%) in esophagus, Stomach and Uterus approximately in equal distribution representing 12 (10.1%) and only 5(4.2%) in lungs.

Distribution of the study sample according to duration, since the diagnosis of disease, showed that 104 (86.7%) between 1-15 months, 13 (10.8%) 16-30 months and 3 (2.5%) 31-60 months.

Patients on the 2nd cycle of chemotherapy were found to constitute 40(33.3%), where those on the 3rd cycle were 38(31.7%), 4th cycle 17(14.2%), 6th 13(10.8%), 5th 10(8.3%), 7th and 8th show same percentage 1(.8%).

The study showed that 83(69.2%) of the study population had not received previous chemotherapy, while 37 patients (30.8%) received pervious chemotherapy.

The most of the participants who were developed diarrheal toxicity revealing that, most patients were in grade (1) 79.8%, while only about 9% of them were having, grade (2), grade (3) and grade(4) approximately had equal distribution representing 5.6%. Four patients developed oral mucositis had equal distribution representing 50% in grade1 and, grade2.

In another study done by Sonis ST, et al. at 2001; the total of 24 courses in which mucositis developed, the percentages of grade I, II and III mucositis were 66.7%, 20.8% and 12.5%, respectively. Grade IV mucositis was observed in none of the cases.[7]

In the results there was no associations detected between gender, age, pervious chemotherapy, current cycle of chemotherapy and gastrointestinal mucositis toxicity, grades of gastrointestinal mucositis toxicity, respectively.

Further studies must be carried out in 5-fluorouracil regimen treatment to reduced it’s side effects, specially gastro intestinal Mucositis.

CONCLUSION

In the results found there is no associations were detected between gender, age and pervious chemotherapy, current cycle of chemotherapy and severity of gastrointestinal mucositis toxicity occurring grades, respectively.

Recommendation

Further studies are needed to determine severity of 5-fluorouracil induced gastro intestinal Mucositis to reduce it's occurring.

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