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Pharmacological Evaluation of 5-Flurouracil (5-FU) Utilization among Patients with Gastro-Intestinal Tract (GIT) Cancers

التقييم الدوائي لدواء "فلوروبراسيل" بين المرضى المصابين بسرطان الجهاز الهضمي

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Abstract

The clinical utilization of 5-Fluorouracil and its therapeutic implications were investigated at Al-Watani governmental hospital at Nablus (Palestine). The drug and disease profiles of one hundred and thirty patients suffering from various types of cancers were studied. No correlation was noticed between gender and cancer in general although such correlation might exist among patients with gastrointestinal tract (GIT) cancers. Approximately one third (29%) of those patients were suffering from (GIT) cancers especially colon and liver cancers. The majority (66%) of the patients with GIT cancers were treated with 5-FU. Leucovorin (LV) was used by (68%) of patients suffering from GIT cancers and were receiving 5-FU. Patients, in general, were not exposed to poly-chemotherapy (2.6 drugs/patient). Strong pain killers like morphine were used in approximately 24% of patients having GIT cancers. The utilization of 5-FU and LV is in agreement to the general international recommendations especially among patients with colon cancer. Further national studies are required to investigate cost/effectiveness, dose and drug appropriateness among patients with malignant diseases.

ملخص

لقد تم بحث الاستعمال السريري والمغزى العلاجي لدواء فلوروبراسيل في المستشفى الوطني الحكومي في مدينة نابلس في فلسطين، وتمت الدراسة على الملف الدوائي والمرضي لمائة وثلاثين مريضاً مصابين بالسرطان. لم تكن هنالك علاقة بين الأصابة بالسرطان وجنس المريض، مع أنه قد توجد مثل هذه العلاقة في حالة سرطان الجهاز الهضمي.وكان حوالي ثلث المرضى تقريباً (٢٩%) يعانون من سرطان الجهاز الهضمي، وخاصة سرطان القولون والكبد. وكانمعظم مرضى سرطان الجهاز الهضمي (٦٦%) يتناولون دواء فلوروبراسيل، كما أن ٦٨% من هؤلاء المرضى كانوا يتناولون دواء لوكوفرين (LV). ولم يكن عند مرضى

السرطان، بشكل
عام، ظاهرة تعدد الأدوية، وانما كان معدل استهلاكهم للدواء ٢,٦ دواء لكل مريض. وقد استعملت المسكنات القوية مثل المورفين عند ٢٤% من المرضى المصابين بسرطان الجهاز الهضمي. ويتفق استعمال دواء الفلوروبراسيل والكوفرين مع التوصيات الدولية العامة، وخاصة في سرطان القولون وهناك حاجة إلى المزيد من الدراسات لتحديد الفعالية مقابل التكلفة، وكذلك دراسة الجرعة ونوعية الأدوية المستعمله وتعد مدى مناسبتها أمراً مطلوباً على المستوى الوطني.

Introduction

According to the health statistical survey carried out in the year 2000 in Palestine, it is estimated that 0.1% of people in Palestine suffer from malignant diseases [(1)]. It is also estimated that the main causes of death in Palestine are cardiovascular diseases with 12.8 followed by malignancies with 11.2 % of the total number of deaths among the elderly above the age of 60 years [(2)]. This justifies the need for more involvement of health professionals from all specializations in cancer pharmacotherapy research. In north Palestine, there is a central oncology unit located in Al-Watani hospital that serves all the residents of north Palestine. The aim of this study which was carried out in that unit is to investigate the utilization pattern of chemotherapeutic agents in general and 5-fluorouracil (5-FU) in particular. Our focus would be on the types of cancers for which 5-FU is used and on the types of adjunct drugs used in combination with 5-FU.

The significance of such study is to evaluate whether the pattern of 5-FU utilization in Palestine deviates from or resembles those recommended by published literature. The 5- fluorouracil (5-FU) is a chemical analogue of uracil with a fluorine atom at the C-5 position in place of hydrogen [(3)] (Figure 1). The drug rapidly enters the cell using the same facilitated transport mechanism as uracil [(4)]. Inside the cells, 5-FU is converted to several active metabolites: fluorodeoxyuridine monophosphate (FdUMP), fluorodeoxyuridine triphosphate (FdUTP) and fluorouridine triphosphate (FUTP) which disrupt RNA synthesis and the action of thymidylate synthase enzyme (TS) [(5-7)]. The rate-limiting enzyme in 5-FU catabolism is dihydropyrimidine dehydrogenase (DPD),

which converts 5-FU to dihydrofluorouracil (DHFU) [8-10]. The drug is widely used in the treatment of a range of cancers, including colorectal and breast cancers, and cancers of the aerodigestive tract.

Although 5-FU in combination with other chemotherapeutic agents improves response rates and survival in breast, head and neck cancers, it is in colorectal cancer where 5-FU has had the greatest impact [11]. Leucovorin (LV; 5'-formyltetrahydrofolate) is a drug that is frequently used in conjunction with 5-FU. Leucovorin is not a chemotherapeutic drug itself; however it is an adjunct to chemotherapy drugs. LV is a compound similar to folic acid**,** which is a vital vitamin. It has been used to expand the intracellular concentration of reduced folate (CH_2THF) and has been shown to increase the *in vitro* and *in vivo* toxicity of 5-FU in many cancer cell lines [12– 14]. High intracellular levels of the reduced folate CH_2THF are necessary for optimal binding of FdUMP to TS. Leucovorin enters the cell via the reduced folate carrier and is converted to CH_2THF, which is then polyglutamated by folylpolyglutamate synthetase. Polyglutamation increases the cellular retention of CH_2THF and enhances the stabilization of its ternary complex with TS and FdUMP [15-18]. The advanced colorectal cancer meta-analysis project (ACCMP) showed that 5-FU/LV generated significantly superior response rates compared with bolus single-agent 5-FU (23% versus 11%); however, this did not result in improved overall survival [19].

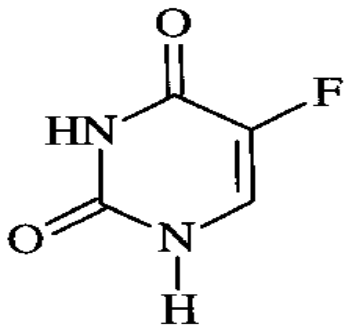

Figure (1): Chemical structure of 5-FU

Methodology

The full drug and disease profiles of one hundred and thirty patients attending the oncology unit at AL-Watani governmental clinic in Nablus (north of Palestine) and receiving chemotherapeutic medications were reviewed and recorded. Those one hundred and thirty patients represent all the patients receiving chemotherapeutic medications and attending that clinic at the time of study. The access to the files was made by a pre-approval from the ministry of health and the personnel working in the oncology clinic. Extraction of the data from the files was made by one of the working personnel in the unit who was assigned to us by the ministry of health to facilitate this research. The data in the files concerning age, sex, prescribing physician, diagnosis and medications were all entered in SPSS 10 for windows and consequently analyzed.

Results

The study was carried on one hundred thirty patients receiving chemotherapy at the oncology unit in a governmental hospital in north Palestine. The average age of the patients was 59 years (St. d = 19; range = 90). Gender distribution of the patients shows that males represent 52.3% and females represent 47.7% of the patients. Analysis of the types of cancers which classified according to the affected organ shows that gastrointestinal cancers (GIT) were the most common type followed by breast cancer as can be seen in Table 1.

Table (1): Frequency and Percentage of some cancer types present in the oncology unit.

Types of Cancer	Frequency	Percentage
GIT	38	29.23%
Colon	12	
Esophagus	1	
Liver	11	
Naso-Pharynx	1	
Pancreatic	5	
Stomach	7	

… Continue table no. (1)

Types of Cancer	Frequency	Percentage
Tongue	1	
Breast	23	17.69%
Lung	8	6.15%
Kidney	4	3.07%
Bladder	16	12.30%
Prostate / testicular	5	3.84%
Brain	5	3.84%
Blood (Hodgkin & non-Hodgkin lymphoma)	12	9.23%
Uterine / ovary	5	3.84%
Skin	2	1.53%
Endocrine (Thyroid)	1	0.76%
Muscle / Fibrous Tissue	4	3.07%
Others	7	5.38%

Among the GIT cancers, the most common type was colon cancer followed by liver cancer. Analysis of drugs utilized showed that the one hundred thirty patients were receiving a total of three hundred and forty two chemotherapeutic drugs with an average of 2.6 drug per patient (St. d. = 1.1; minimum = 1; maximum = 6 drugs). The most commonly used chemotherapeutic agent among the patients. Fourty one patients out of one hundred thirty (41/130; 31.5%) were receiving 5-FU. This drug was used among 66% of patients suffering from GIT cancers. The type of cancers for which 5-FU was utilized is shown in Table 2.

Table (2): Types of cancers treated with 5-FU as seen in the oncology unit.

Type of Cancer	Number of patients receiving 5-FU
Breast	13
GIT	25 (9 colon; 1 esophagus; 5 liver; 1 naso-pharynx, 3 pancreas, 6 stomach)
Uterine	1
Lung	1
(Blood) Non-Hodgkin	1

Analysis of other drugs co-prescribed with 5-FU showed that Lecuoverin was the most commonly co-prescribed drug with 5-FU. Nineteen patients out of one hundred thirty (19/130; 14.6%) were receiving both 5-FU and Leucoverin. Among patients with GIT cancers, seventeen patients out of twenty five (17/25; 68%) were using 5-FU/LV combination. The types of cancers for which both 5-FU and leucoverin were given is seen in Table 3.

Table (3): Types of cancers treated with 5-FU/LV combination.

Type of Cancer	Number of Patients receiving (5-FU + Leucovorin)	Percentage
Colon	9 / 12	75.0%
Esophagus	1 / 1	100.0%
Hodgkin / non-Hodgkin	2 / 12	16.7%
Liver	3 / 11	27.7%
Pancreatic	2 / 5	40.0%
Stomach	2 / 7	28.6%

Discussion

Because of the limited health and financial resources available in Palestine, efforts of researchers in the field of pharmacotherapy should be maximized and directed toward proper use of these limited resources and implementation of international therapeutic guidelines in treating diseases. This study sheds some light on the therapeutic practices at a major oncology unit in a governmental hospital in North Palestine. Unfortunately, the authors could not find similar publications on 5-FU in the neighboring countries for the purpose of comparison. In the sample studied, there was insignificant correlation between gender and cancer in general. However, among the patients with GIT cancers, there were 16/38 males and 22/38 females suggesting a possible gender correlation. The results further indicate that GIT cancers are being the most common type of cancers encountered in the oncology unit at the time when the study was carried out. The most commonly utilized chemotherapeutic drug especially in colon cancer is 5-FU. It is largely supported by a large

bulk of literature data indicating the usefulness of this drug in colon cancer [20].

Leucovorin, an adjunct, non-chemotherapeutic drug was also used as recommended by literature in combination with 5-FU for the treatment of colon cancer [21]. Thirteen patients with GIT cancers were not receiving 5-FU and were treated with other chemotherapeutic agents like cisplatin, cyclophosphamide, vinblastin, bleomycin and mitomycin. Cisplatin was the most common alternative to 5-FU. Cispaltin was used for three patients with liver cancer and three patients with stomach cancer. Strong opioid analgesics were used by nine patients with GIT cancers. Assuming that receiving more than three drugs of different classes with different mechanisms is considered polytherapy, our study shows that patients attending the oncology unit were not subject to polychemotherapy (2.6 drugs per patient) with the bulk of patients (more than 69%, data not shown) were receiving one or two chemotherapeutic drugs. The lack of polychemotherapy can be advantageous in one hand since it will minimize the exposure to adverse effects and it can be disadvantageous because one or two chemotherapeutic drugs might not be enough to eradicate resistant subclones of cancer.

The use of 5-FU for breast cancer was also noticeable (13/23, > 50%). Several studies have indicated the usefulness of 5-FU alone or in combination with other chemotherapeutic agents in the treatment of breast cancers [22- 23].

The medical files of the patients indicated that some of the patients were followed for other types of cancers suggesting that those patients might have metastasis at a certain time during 5-FU chemotherapy. This suggests that 5-FU might not effective in treating or stopping cancer metastasis. Unfortunately, most of the medical files which contain the cancer history of the patients did not indicate the stage of colon cancer upon time. The lack of this piece of data disables us from judging whether the 5-FU changed the stage of colon cancer.

This study indicated that the treatment of colon cancer with 5-FU among the patients studied in the sample was in accordance with the recommended published literature and guidelines which states that 5-FU

increases the survival rate among patients with colon cancer [14-23]. A very important recommended guideline is to screen patients who are at high risk of developing colon cancer [25]. This study should initiate screening programs among Palestinians for possible risks of colon cancer and should initiate other studies to evaluate the appropriateness of this drug. Dosage regimens for other types of cancers should also be carried out at the national level with emphasis on cost/effectiveness as well as adherence to international recommendation regarding their therapy.

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