IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 6 Ver. XIV (June 2016), PP 134-137
www.iosrjournals.org

Therapeutic Drug Monitoring of 5-Fluorouracil In Teritiary Care Teaching Hospital

Alapati Yedukondala Rao2*, Gouthami, Ayesha, Nagesh Adla, Goverdhan Puchchakayala[1]

[1]*Department of Clinical Pharmacy, Vaagdevi College of Pharmacy, Ramnagar,Hanamkonda, Warangal – 506002, Telangana, INDIA.*

[2]*Department of Oncology, Kakatiya Medical College, MGM Hospital, Warangal – 506002, Telangana, INDIA.*

Abstract: *5-Fluorouracil (5-FU) is the basis of most combination chemotherapies for gastrointestinal tumours and breast cancers. It is generally well tolerated, but side-effects might require dose-adjustment. As adverse events are not specific to the 5-FU component of the chemotherapy-combination, i.e. neutropenia, diarrhoea or cardiotoxicity, the knowledge of 5-FU plasma levels might help to attribute these side effects to the 5-FU compound. The optimal concentration-range (AUC, area under the curve) has been described to be within 20-25mgh/l. The aim of this study was to determine the concentrations of 5-FU in plasma for routine therapeutic drug monitoring. High performance liquid chromatography (HPLC) had been used for the determination of 5-FU in human plasma.*

Methods: *36 samples were collected and 28 samples from breast cancer patients and 8 samples from gastrointestinal patients. treated with 5-FU infusional regimes, Venous blood(3ml) was collected into heparinised tubes. The tubes was immediately centrifuged at 3000rpm for 10min at 4 ºC. Resulting plasma supernatants was transferred to individual 3 ml polypropylene tubes and was frozen in freeze. The frozen tubes was transferred to the laboratory once a day at -20 ºC. 5- fluorouracil plasma concentrations was analysed by high performance liquid chromatography using UV detection(wavelength=262nm).Methods which had been used for determination of 5-FU injection were HPLC. The method developed in this study is simple, rapid, economical, and accurate, and it is applied for rapid determination of 5-FU in injection and human plasma.*

Results: *Of the total, 14 were male patients (38.88%) and 22 (61.11%) were female patients. The mean age of male population was 56.13±10.20 years, and the mean age of female population was 53.43±12.01years and Among 36 patients,7 patients were diagnosed with breast cancer left,11 patients with breast cancer right and 18 patients were diagnosed with gastrointestinal cancer. The steady state plasma drug concentrations were measured and differentiated based on their weights. Patients with the weight between50-60 kgs the steady state plasma concentration measured were 161.9±9.828µg/dl and Patients with the weight between 61-80 kg the steady state concentration measured were109.77±8.485µg/dl.*

Conclusion*: Among 36 patients , those patients with low body weight (50-60 kgs) were found with elevated plasma drug concentration and those patients with increased body weight(61-70kgs) were found with reduced steady state concentration. Hence we conclude that dosing should be done based upon body weight.*

Keywords: *5-fluorouracil,Therapeutic Drug Monitoring, High Performance Liquid Chromatography.*

I. Introduction

Therapeutic drug monitoring (TDM) has contributed substantially in assisting patient management and has become an important tool in clinical medicine (1). Measurement of patient's serum or plasma taken at appropriate time after drug administration (2). Despite being one of the oldest anticancer drugs 5-FU is considered not only as the standard drug for the treatment of breast, head and neck cancers, gastrointestinal cancers and also used for colorectal cancers (3). The fluorouracil (5-FU) is an anticancer agent used in the treatment of solid tumours. This drug, an analogue of the natural pyramidine uracil, must be converted to the nucleotide to exert its effect. The drug is rapidly metabolized after administration, giving cytotoxic fluronucleotides with well-known antineoplastic properties (4). The mechanism of 5-FU cytotoxicity is complex because the drug is activated through different pathways leading to atleast three cytotoxic compounds: fluorodeoxyuridine monophosphate, which inhibits thymidylate synthase and subsequent DNA synthesis; fluorouridine triphosphate, which is directly incorporation into DNA(5). 5-FU injection is widely used and many products with the specification of 0.25gms/10ml. Although 5-FU is an active medicine against many cancers, it has some side effects. Some of the most common and important side effects include soreness of the mouth, difficulty in swallowing, diarrhoea, stomach pain, low white blood counts and anaemia (6).It has proven that if there were large amounts of 5-FU in human plasma after injecting for certain hours, 5-FU would not metabolise completely and would endanger health (7). 5-FU is known to have a narrow therapeutic index: High levels can lead to severe side effects, whilst low levels will miss a therapeutic effect. Side effects of 5-FU which

frequently lead to dose adjustment are diarrhoea (CI), neutropenia (bolus) and hand/foot syndrome (CI) (8). It has proven that if there were large amounts of 5-FU in human serum after injecting for certain hours, 5-FU would not metabolise completely and would endanger health (9). Therefore, developing a simple rapid economical and accurate method for the determination of 5-FU in human serum is necessary if dose adjustment for toxic side effects is necessary (10). Therefore, developing a simple rapid economical and accurate method for the determination of 5-FU in human serum is necessary. So far, gas chromatography-mass spectrometry (GCMS), high performance liquid chromatography (HPLC) had been used for the determination of 5-FU in human plasma (7).

II. Material And Methods

The prospective experimental study was carried out in oncology department of Mahatma Gandhi Memorial Hospital (MGMH), Warangal, Telangana, India for a period of 6 months. For the study, ethical clearance was obtained from the human ethical committee. Data collection was performed according to hospital regulations after the approval by the Hospital administration/ethical committee. The study population contain 36 cancer (breast/GIT) cases reviewed between the considered study periods. The patients with other illnesses and age below 18,age above 75 and pregnant ladies are excluded. The 3ml blood sample was taken into ependroff tubes and the samples were stored in freeze. The blank plasma was stored at -20^{o} C and used for method development and validation. A series of drug (5-FU) was prepared in double distillled water and 500µl plasma was spiked with 50 µl drug solutions to prepare specific concentration range. To the plasma sample 500µl of 10% v/v perchloric acid solution was added and vortexed for 10 minutes. The precipitated samples were centrifuged (centrifuge machine) at 3500 rpm for 15 minutes. The clear supernatant layer was separated in neat and dried amber glass vials. The extracted drug solution (20 µl) was injected directly into the HPLC system.

III. Sample Collection

After 1 hours of drug infusion, venous blood (2ml) was collected into heparinised tubes. The tubes were immediately centrifuged at 3000 rpm for 10 mins at 4^{0}C. Resulting plasma supernatants was transferred to individual 3 ml polypropylene tubes and frozen in freeze. The frozen tubes was transferred to the laboratory once a day at -20^{0}C[7] .

Statistics:

Sample was analysed using HPLC. Peak area and peak height was determined. The pharmacokinetic parameters like Area under Curve (AUC), Clearance, Rate of elimination were calculated using kinetica and SPSS software. Mean values and Standard deviation were calculated using graph pad prism6.0 & SPSS version 12.0.

IV. Results And Discussion

Of the total, 14 were male patients (38.88%) and 22 (61.11%) were female patients. The mean age of male patients was 56.13±10.20 years, and the mean age of female patients was 53.43±12.01 years.

GENDER	MEMBERS	PERCENTAGE
MALES	14	38.88%
FEMALES	22	61.11%

Table 1: Gender distribution among cancer patients

Among 36 patients, 18 patients were diagnosed with breast cancer ,18 patients were diagnosed with gastrointestinal cancer.

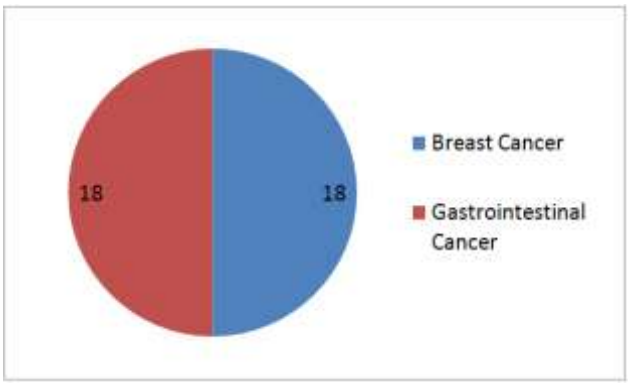

Fig: 1: Types of cancer

Table 1: The steady state plasma drug concentrations were measured and differentiated based on their Body Surface Area(BSA)..

S.No	Age	Sex	BSA	Type of cancer	Plasma drug concentration
1	48	Female	1.54 m^2	Breast cancer	168.3µg/ml
2	73	Male	1.52 m^2	Gastrointestinal cancer	175.5µg/ml
3	51	Female	1.63 m^2	Breast cancer	140.3µg/ml
4	36	Female	1.8 m^2	Gastrointestinal cancer	173.9µg/ml
5	43	Female	1.54 m^2	Breast cancer	162.3µg/ml
6	32	Female	1.48 m^2	Breast cancer	175.7µg/ml
7	65	Male	1.51 m^2	Gastrointestinal cancer	171.7µg/ml
8	54	Female	1.48 m^2	Breast cancer	169.6µg/ml
9	43	Female	1.62 m^2	Breast cancer	154.3µg/ml
10	69	Female	1.8 m^2	Breast cancer	174.91µg/ml
11	53	Female	1.63 m^2	Breast cancer	173.3 µg/ml
12	41	Female	1.53 m^2	Breast cancer	166.97µg/ml
13	37	Male	1.59 m^2	Gastrointestinal cancer	160.87µg/ml
14	28	Female	1.51 m^2	Breast cancer	173.7µg/ml
15	41	Male	1.63 m^2	Gastrointestinal cancer	135.92µg/ml
16	75	Female	1.62 m^2	Breast cancer	136.98µg/ml
17	49	Female	1.63 m^2	Breast cancer	132.7µg/ml
					161.9±9.828µg/ml

S.No	Age	Sex	Body Surface Area	Type of cancer	Plasma drug concentration
18	60	Male	1.71m^2	Gastrointestinal cancer	127.7µg/ml
19	56	Male	1.8 m^2	Gastrointestinal cancer	100.3µg/ml
20	51	Female	1.81 m^2	Breast cancer	103.78µg/ml
21	73	Male	1.69 m^2	Gastrointestinal cancer	125.5µg/ml
22	68	Male	1.72 m^2	Gastrointestinal cancer	100.07µg/ml
23	41	Female	1.81 m^2	Breast cancer	100.2µg/ml
24	72	Male	1.71 m^2	Gastrointestinal cancer	112.4µg/ml
25	67	Female	1.86 m^2	Breast cancer	99.87µg/ml
26	78	Female	1.64 m^2	Breast cancer	136.01µg/ml
27	56	Male	1.71 m^2	Gastrointestinal cancer	124.9µg/ml
28	61	Male	1.86 m^2	Gastrointestinal cancer	112.4µg/ml
29	61	Male	1.86 m^2	Gastrointestinal cancer	100.64µg/ml
30	62	Female	1.81 m^2	Gastrointestinal cancer	99.09µg/ml
31	63	Male	1.79 m^2	Gastrointestinal cancer	99.65µg/ml
32	53	Female	1.7 m^2	Gastrointestinal cancer	103.5µg/ml
33	72	Female	1.9 m^2	Breast cancer	96.63µg/ml
34	62	Female	1.86 m^2	Gastrointestinal cancer	101.8µg/ml
35	76	Female	1.9 m^2	Breast cancer	98.5µg/ml
36	39	Male	1.64 m^2	Gastrointestinal cancer	128.9µg/ml
On avg					109.77±8.485µg/ml.

Our study on TDM On 5-fluorouracil shows that body weight should be considered for dose adjustment in oncology and steady state plasma drug concentration in obese is lower when compare to normal levels. A study in Germany (Martina Blaschke et al) stated that most anticancer drugs are characterised by a narrow therapeutic window: a small change in dose can lead to poor anti-tumour effects or an unacceptable degree of toxicity (6). This study is similar to our trial.In this study patients those patients with dose according to body weight were reached the therapeutic target,those patients with low body weight the drug concentration measured was above the normal range and those patients with high

V. Conclusion

The association between toxicity and high 5-FU plasma levels has been reported in many studies and Effective therapeutic drug monitoring of cytotoxic agents could prevent the consequences of treatment failure in drug sensitive cancers.

References

[1]. Seop K, Lee H, Overview of Therapeutic Drug Monitoring, Korean Journal of Internal Medicine 2009 March; 24(1),1–10.
[2]. Kulishov S, Lakovenko O,Therapeutic drug monitoring- an overview of commonly monitored drugs, International journal of pharmacology and pharmaceutical Technology, April2012,1(1),2277-3436.
[3]. Casale F,Canaparo,Plasma concentration of 5-Fluorouracil and its metabolites in colon cancer patients,pharmacol res,2004aug:50(2):173-9.
[4]. Ning Z,Ying Y,5-Fluorouracil:Mechanism of Resistance and reversal strategies,molecules 2008,13,1551-1569
[5]. 5.Zing Z,Shen J,Determination of 5-fluorouracil injection and human serum by HPLC,Journal of food and drug analysis, 2012,20(4), ,947-950.

[6]. Gaurav G ,James J,Pharmacokinetically guided dose adjustment of 5-Fluorouracil- A critical element toward personalized medicine,Clinical colorectal cancer,march 2014,13,123-32.
[7]. Wasif M,Adrienne C,Pharmacokinetically guided dose adjustment of 5-fluorouracil:a rational approach to improving therapeutic outcomes, J Natl Cancer Inst 2009;101: 1543 – 1552.
[8]. Zing Zhu,Gui-Jun Shen,Determination of 5-fluorourcil injection and human serum by HPLC,Journal of food and drug nalysis,vol.20. no.4,2012,947-950.
[9]. Muhammad Usman Minhas,Mahmood Ahmad*, Development and Optimization of Fast and New Reversed-Phase HPLC Method for Analysis of 5-Fluorouracil Human and Rabbit Plasma, Pakistan Veterinary Journal,2014,35,71-75.
[10]. Martina B, Jutta B, Ulrike W,Measurements Of 5-Fluorouracil Plasma Concentrations in Patients with Gastrointestinal Cancer:5-Fluorouracil Levels Reflect The 5-Fluorouracil Dose Applied, Journal Of Cancer Therapy, 2012,3,28-36.