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Effect of Cytotoxic Medications (MTX, Cisplatin, 5 FU and cyclophosphamide against creatinine clearance Patient Relationships And Creatinine clearance Urea with Cancer Patients.

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Research Article

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Abstract

Various treatments performed for this disease such as surgery, chemotherapy, radiotherapy, hormone therapy and immunomodulators. Before treatment is done well or let the patient's condition as stable as it was the chemotherapy. Than chemotherapeutic drugs that are excreted through the kidneys so as to affect kidney function. Methotrexate, cisplatin, 5 fluorouracil and cyclophosphamide is a cytotoxic drug that is often present in the chemotherapy protocol.

Objectives: This paper reports how the effect of cytotoxic drugs (MTX, cisplatin, 5 FU and cyclophosphamide to the patient as well as creatinine clearance relationship with creatinine clearance of urea cancer patient.

Methology: The research was conducted using longitudinal study design and methods of a prospective evaluation in patients used MTX/Cisplatin/5-FU/Cyclophosphamide in the oncology ward HUSM during stay in Hospital.

Result: This paper reports how the effect of cytotoxic drugs (MTX, cisplatin, 5 FU and cyclophosphamide to the patient as well as creatinine clearance relationship with creatinine clearance of urea cancer patient.

Keywords: *Creatinine clearance, methotrexate, cisplatin, 5 fluorouracil, cyclophosphamide*

Introduction

Cancer is a disease that most cannot be avoided; do not know the age, age, race and social. Various treatments performed for this disease such as surgery, chemotherapy, radiotherapy, hormone therapy and immunomodulators[1]. Before treatment is done well or let the patient's condition as stable as it was the chemotherapy[2]. Than chemotherapeutic drugs that are excreted through the kidneys so that it will to influence renal function as well. Methotrexate, cisplatin, 5 fluorouracil and cyclophosphamide is a cytotoxic drug that is often present in the chemotherapy protocol[3]. In general, the calculation of creatinine clearance will be done before the administration of drugs.

Methotrexate

Methotrexate was originally developed and continues to be used for chemotherapy either alone or in combination with other agents. It is effective for the treatment of a number of cancers including: breast, head and neck, leukemia, lymphoma, lung, osteosarcoma, bladder, and trophoblastic neoplasms[1]. Half life 3-10 hr for low-dose cancer, 8-15 hr for high-dose. Peak plasma time PO: 1-2 hr, IM: 30-60 min . Volume distribution : Initial: 0.18 L/kg Steady-state: 0.4-0.8 L/kg Bioavailability: dose-dependent; 60% at doses <30 mg/sq.meter, significantly less at >80 mg/sq.meter.Protein Bound: 50%Metabolism: hepatic & intracellularMetabolites: polyglutamated forms Excretion: urine 80-90% within 24 hr. Mechanism of action: Inhibits dihydrofolic acid reductase: interferes with DNA synthesis, repair, & cellular replication.Mechanism of Action :Inhibits dihydrofolic acid reductase: interferes with DNA synthesis, repair, & cellular replication.[4]

Cisplatin

Cisplatin is a major antineoplastic drug used for the treatment of solid tumors. Cisplatin side effect is nephrotoxicity. Cisplatin Uptake into Renal Cells Uptake of cisplatin is mainly through the organic transporter pathway. The kidney accumulates cisplatin to a greater degree than other organs and is the major route for its excretion. The cisplatin concentration in proximal tubular epithelial cells is about 5 times the serum concentration.[2] The disproportionate accumulation of cisplatin in kidney tissue contributes to cisplatin-induced nephrotoxicity.[3]

Mechanism of action cisplatin is platinum coordination compound that inhibits DNA synthesis; cross-links and denatures strands of DNA; disrupts DNA function by covalently binding to DNA bases; can also produce DNA intrastrand cross-linking and breakage not a true alkylating agent. Pharmacokinetics cisplatin are Half-life elimination (terminal): 24hr to 47 days, Protein bound: >90%, Excretion: Urine (90%); feces (10%), Clearance: 15 L/hr/m²,Vd: 11 L/m².[5]

5-Fluorouracil

5-fluorouracil (5-FU) is a potent anticancer agent; its clinical use is limited for its marked hepatotoxicity and nephrotoxicity.[6] Pharmacokinetics 5 FU are Half-Life: 16 min, Onset: 2-7 d, but may take up to 12 wk, Duration: 24 hr, Metabolism: liver, Metabolites: urea, fluorouracil, dihydrofluorouracil, expired CO2 metabolite, Excretion: urine[7]

Cyclophosphamide

Cyclophosphamide is an extensively used anticancer and immunosuppressive agent.[8] Mechanism of action cyclophosphamide is metabolites interfere with malignant cell growth by cross-linking tumor cell DNA; dose not have specificity for any phase of the cell cycle; also has potent immunosuppressive activity. Absorption : Bioavailability: 75% peak Plasma Time: 1 hr (cyclophosphamide); 2-3 hr (metabolites). Metabolism : hepatic metabolites: 4-hydroperoxycyclophosphamide; 4 aldophosphamide. Elimination : Half-Life: 3-12 hr, Excretion: Urine, Onset: 2-3 hr, Vd: 0.48-0.71 L/kg.[9]

Creatinine is a chemical waste molecule that is generated from muscle metabolism. Creatinine is produced from creatine, a molecule of major importance for energy production in muscles. Approximately 2% of the body's creatine is converted to creatinine every day. Creatinine is transported through the bloodstream to the kidneys. The kidneys filter out most of the creatinine and dispose of it in the urine. Creatinine is mainly filtered by the kidney, though a small amount is actively secreted. There is little-to-no tubular reabsorption of creatinine. If the filtering of the kidney is deficient, blood levels rise. As a result, creatinine levels in blood and urine may be used to calculate creatinine clearance (ClCr), which reflects the glomerular filtration rate (GFR) [11].

Creatinine is made at a steady rate and is not affected by diet or by normal physical activities. If your kidneys are damaged and cannot work normally, the amount of creatinine in your urine goes down while its level in your blood goes up. Three types of tests on creatinine can be done [11]:

Blood creatinine level

The blood creatinine level shows how well your kidneys are working. A high creatinine level may mean your kidneys are not working properly. The amount of creatinine in the blood depends partly on the amount of muscle tissue you have; men generally have higher creatinine levels than women.

Creatinine clearance test

A creatinine clearance test measures how well creatinine is removed from your blood by your kidneys. A creatinine clearance test gives better information than a blood creatinine test on how well your kidneys are working. A creatinine clearance test is done on both a blood sample and on a sample of urine collected over 24 hours (24-hour urine sample).

Blood urea nitrogen-to-creatinine ratio (BUN:creatinine)

The levels of blood creatinine and blood urea nitrogen (BUN) can be used to find the BUN-to-creatinine ratio [2-4]. A BUN-to-creatinine ratio can help your doctor check for problems, such as dehydration, that may cause abnormal BUN and creatinine levels. Urea is a waste product made when protein is broken down in your body[10]. Urea is made in the liver and passed out of your body in the urine. A blood urea nitrogen (BUN) test measures the amount of urea in your blood[11]. Like creatinine, it can help your doctor see how well your kidneys are working.

Creatinine is made at a steady rate and is not affected by diet or by normal physical activities [9-8]. If your kidneys are damaged and cannot work normally, the amount of creatinine in your urine goes down while its level in your blood goes up [1].

High creatinine blood levels : High creatinine blood levels can mean serious kidney damage or disease is present. Kidney damage can be caused by a life-threatening infection, shock, cancer, or low blood flow to the kidneys[12]. Other conditions that can cause high blood creatinine levels include blockage of theurinary tract (such as by a kidney stone), heart failure, dehydration, excessive blood loss that causes shock, gout, or muscle conditions (such asrhabdomyolysis, gigantism, acromegaly, myasthenia gravis, muscular dystrophy, and polymyositis). Usually a high blood creatinine level means that the creatinine clearance value is lower than normal.

High creatinine clearance :. High creatinine clearance values can be caused by strenuous exercise, muscle injury (especially crushing injuries), burns, carbon monoxide poisoning, hypothyroidism, and pregnancy [1-7].

The amount of creatinine in the blood depends partly on the amount of muscle tissue; blood creatinine levels are generally higher in men than in women. Also, people who have large muscles, such as athletes, normally have above-average blood creatinine levels.

The creatinine clearance is estimated using the Cockcroft-Gault formula[12,13]:

$$C_{cr}(ml/min) = \frac{(140 - \text{Age years}) \times \text{weight (in kilograms)}}{72 \times S_{cr}(\text{in mg/dL})}$$

Methodology

Conducted a study using longitudinal study designs and methods of prospective evaluation of 9 patients suffering from DLBCL in which 2 patients, 2 patients suffered from lymphoma, a patient suffering from T-ALL, one patient suffering from B-ALL, 2 patients suffering from NPC (nasopharingeal cancer), and 1 patients suffering from lung cancer.

Retrieval of data from medical records include quantitative and qualitative data completeness of patient data (such as age, sex, history of present illness, previous medical history, family history, previous drug history, therapeutic measures, diagnosis, physical examination, investigation, examination and laboratory so then transferred to the data extracted and compiled the data collection sheet. Lack of medical records is equipped with a direct look at the patient's condition.

Inclusion: Cancer patients who received cisplatin or methotrexate or 5 - Flurouracil or cyclophosphamide
Exclusion: Patients who are not getting cisplatin or methotrexate or 5 - Flurouracil or cyclophosphamide.

Clinical evaluation of patients before, during and after the administration of medication seen from the laboratory. Data were analyzed descriptively and the number and percentage calculations are presented in tabulated form and diagram the inferential statistics used to calculate significancie.

Results

Two patients with DLBCL with each of the age of 61 years and 67 years to get cyclophosphamide at a dose of 1410 mg and 1237.5 mg. Where patients get a dose of 1410 mg of creatinine clearance is known before the given cyclophosphamide is 108.63 ml / min, while creatinine clearance during cyclophosphamide administration was 95.22 ml / min and after administration of cyclophosphamide was 110.34 ml / min. Patients with a known dose of 1237.5 mg creatinine clearance before being given cyclophosphamide was 64.13 ml / min, for giving cyclophosphamide was 66.11 ml / min and creatinine clearance after being given cyclophosphamide is 87.17 ml / min.
One patient suffering from NPC (Nasopharingeal Cancer) by the age of 43 years to get 5 fluorouracil (5 FU) at a dose of 864.87 mg loading dose followed by maintenance dose for 22 hours is 1296 mg. The patient was known to the creatinine clearance before getting 5 FU was 85.16 ml / min, for a 5 FU was 71.98 ml / min and after a 5 FU was 97.53 ml / min.
One patient who also suffered from NPC (Nasopharingeal Cancer) with 68 years of age get a dose of 70 mg cisplatin. The patient was known to the creatinine clearance before getting cisplatin was 82.51 ml / min.
One patient who suffered from lung cancer by age 54 years to get a dose of 77 mg cisplatin. The patient was known to the creatinine clearance before getting cisplatin was 57.24 ml / min.
One patient who suffered from lymphoma by the age of 53 years to get a dose of 115.5 mg cisplatin. The patient was known to the creatinine clearance before getting cisplatin was 65.05 ml / min and during a cisplatin was 68.27 ml / min.

Table 1. Comparison Crcl –MTX

Characteristic	Mean ± SD	t	P value*
Crcl pre-Mtx	77.120 ± 18.954	9.967	0.000
Crcl during-Mtx	80.997 ± 35.480	6.040	0.001
Crcl post-Mtx	89.513 ± 20.049	8.929	0.003

*Paired T-Test

One patient who also suffered from lymphoma by the age of 19 years to get methotrexate administration for 2 hours at a dose of 460 mg was continued for 22 hours giving a dose of 1840 mg. The patient was known to the creatinine clearance during the administration of methotrexate was 158.24 ml / min.
Any patient who will receive the cytostatic will receive antiemetic drugs, analgesics, antibiotics and antipiretic if needed.

Table 2. Comparison Crcl –Cisplatin

Characteristic	Mean ± SD	t	P value*
Crcl pre-Cisplatin	77.120 ± 19.725	9.453	0.000
Crcl during-Cisplatin	81.426 ± 36.398	5.919	0.001
Crcl post-Cisplatin	90.013 ± 19.174	9.389	0.003

*Paired T-Test

From the table above can be seen comparison CrCl and MTX using Paired T-Test. Creatinine clearance before using methotrexate patient was 77 120 ± 18 954 with a significant P value is 0000 where P <0.05. Creatinine clearance patient during the use of methotrexate is 80 997 ± 35 480 with a P value 0001, while creatinine clearance patient after using methotrexate is 89 513 ± 20 049. with a P value 0003. Of significant value that appears to be a change in creatinine clearance creatinine clerence where improvement is proportional to the decrease in MTX in the body.

Table 3. Comparison Crcl –5 FU

Characteristic	Mean ± SD	T	P value*
Crcl pre-5 FU	76.953 ± 18.873	9.988	0.000
Crcl during-5 FU	81.711 ± 36.241	5.965	0.001
Crcl post-5 FU	89.763 ± 19.049	9.424	0.003

*Paired T-Test

Can be seen from the table above comparison of creatinine clearance and cisplatin using Paired T-Test. Creatinine clearance before patient use Cisplatin is 77 120 ± 19 725 with a significant P value is 0000 where P <0.05. Creatinine clearance patient during the use of cisplatin is 80 997 ± 35 480 with a P value 0001, while creatinine clearance patient after the use of cisplatin is 90 013 ± 19 174. with a P value 0003. Of significant value that appears to be a change in creatinine clearance creatinine clerence where improvement is proportional to the reduction of cisplatin in the body

Table 4. Comparison Crcl –Cyclophosphamide

Characteristic	Mean ± SD	T	P value*
Crcl pre-Cyclophosphamide	76.620 ± 18.914	9.923	0.000
Crcl during-Cyclophosphamide	81.426 ± 36.285	5.937	0.001
Crcl post-Cyclophosphamide	89.263 ± 18.942	9.425	0.003

*Paired T-Test

Can be seen from the table above comparison of creatinine clearance and 5 FU using the Paired T-Test. Creatinine clearance before the patient using 5 FU was 76 953 ± 18 873 with a significant P value is 0000 where P <0.05. Creatinine clearance for a patient using 5 FU was 81 711 ± 36 241 with a P value 0001, while creatinine clearance patient after the use of cisplatin is 89 763 ± 19 049 with a P value 0003. Of significant value that appears to be a change in creatinine clearance creatinine clerence where improvement is proportional to the reduced 5 FU in the body.

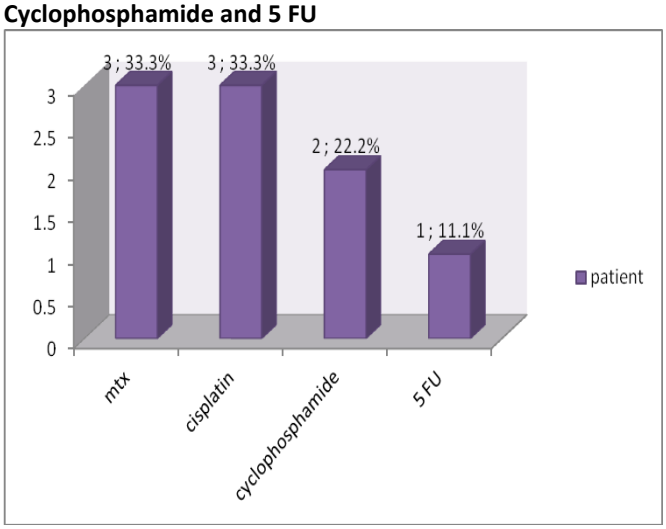
Table 5. Comparison Crcl with Urea

Characteristic	Mean±SD	T	P.value*
Crcl Pre - Urea pre	69.93333 ± 31.16134	3.887	0.060
Crcl During – Urea during	81.02600 ± 43.38968	4.176	0.014
Crcl Post – Urea Post	91.01333 ± 13.73628	11.476	0.008

*Paired t-Test

Can be seen from the table above comparison of creatinine clearance and cyclophosphamide using Paired T-Test. Creatinine clearance before using cyclophosphamide patient was 76 620 ± 18 914 with a significant P value is 0000 where P <0.05. Creatinine clearance were patient during the use of cyclophosphamide 36.285dengan P 81 426 ± 0001 while the creatinine clearance value after using cyclophosphamide patient was 89 263 ± 18 942 with a P value 0003. Of significant value that appears to be a change in creatinine clearance creatinine clerence where improvement is proportional to the reduced cyclophosphamide in the body. From the above table can be viewed with a creatinine clearance of urea pre chemotherapy there was no significant relationship in which the P value> 0.05, while the creatinine clearance during the urea during a meaningful relationship in which the P value 0014 (P value <0.05) and creatinine clearance after chemotherapy with urea also showed a significant association in which the P value 0.08 (P value <0.05).

Graphic 1. Amount Patient Used MTX, Cisplatin, Cyclophosphamide and 5 FU



Graphic 1 illustrates the study found 3 patients using MTX, three patients using cisplatin, 2 patients using cyclophosphamide and 1 patient using 5-FU.

Graphic 1 illustrates the study found 3 patients using MTX, three patients using cisplatin, 2 patients using cyclophosphamide and 1 patient using 5-FU.

Graphic 2. Crcl Patient Used MTX, Cisplatin, 5 FU and Cyclophosphamide

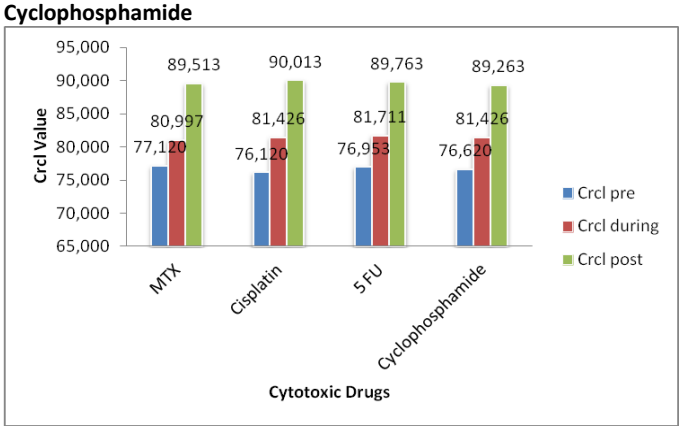


Figure 2 describes the patient pre clearance kreatinine used cytotoxic drug (MTX, cisplatin, 5-FU and cyclophosphamide) on average lower than CrCl during cytotoxic drug used. Clcr during cytotoxic drug used is lower than the cytotoxic drug used Clcr post.

Discussion

In general, studies conducted in patients aged 50 years and over in which age has an influence on an increase in creatinine klirens [10] .Of the study also looked at a lot of hematological diseases (DLBCL, T-ALL, B-ALL, and lymphoma). Comparison between Clcr with cytotoxic drug (MTX, cisplatin, 5-FU and cyclophosphamide) using statistical analysis paired t-test showed a significant effect in which the P value <0.05. From studies conducted creatinine clearance is known that patients on average before receiving cytostatic drug is lower than during and after receiving the cytostatic drug. Where to MTX chemotherapy pre Clcr patient is 77 120 ml / min, during chemotherapy was 80 997 ml / min, and post-chemotherapy was 89 513 ml / min. For the patient pre Clcr Cisplatin chemotherapy was 76 120 ml / min, during chemotherapy was 81 426 ml / min and post chemotherapy was 90 013 ml / min. To 5-fluorouracil chemotherapy pre Clcr patient is 76 953 ml / min, during chemotherapy was 81 711 ml / min and post chemotherapy was 89 763 ml / min.

To cyclophosphamide chemotherapy pre Clcr patient is 76 620 ml / min, during chemotherapy was 81 426 ml / min and post chemotherapy was 89 263 ml / min. This is probably due to the high urea before chemotherapy. Urea is high due to the destruction of body protein due to cancer in patient [12, 13]

Conclusion

MTX, Cisplatin, 5-FU and cyclophosphamide are drugs that pass through renal excretion. Kreatinine clearance patient before chemotherapy is lower than after chemotherapy due to urea patient before chemotherapy was also higher than after chemotherapy. High Urea is one of them caused damage to proteins of cancer suffered by the patient. Cytotoxic drugs also provide a significant effect on creatinine clearance patient, it is seen from the relationship statistical analysis paired t-Test.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests