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Original Article

Effect of R-CHOP Chemotherapy on Creatinine Clearance in Diffuse Large B-Cell Lymphoma

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Abstract

Background : Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (LNH). First-line therapy for DLBCL is a combination regimen of Rituximab, Cyclophosphamide, Hydroxydoxorubicin, Vincristine (Oncovin), and Prednisone (R-CHOP). The CHOP regimen causes acute kidney injury (AKI) directly or mediated by reactive oxygen species (ROS). AKI is associated with significant morbidity and mortality in cancer patients, including high mortality, increased hospitalization, and a lower cancer remission. The aims of this study was to analyzing the effect of R-CHOP chemotherapy on creatinine clearance values in DLBCL lymphoma patients

Methods : Analytical observational study with a retrospective design involved 38 patients diagnosed with DLBCL who underwent R-CHOP chemotherapy at RSUP Dr. Kariadi Semarang. The independent variable of the study was the frequency of chemotherapy. The dependent variables of the study were serum creatinine levels and creatinine clearance which were measured in 4 phases, namely before, post 3x-, post 4x- and post 5x- R-CHOP chemotherapy. Analysis used the Friedman, T-dependent, and Wilcoxon tests.

Results : The creatinine clearance value of DLBCL lymphoma patients before administering R-CHOP had a normal value with an average of 68.98 mL/min. The creatinine clearance value of DLBCL lymphoma patients after administering R-CHOP after 3x chemotherapy was found to be an average of 78.26 mL/min, after 4x chemotherapy the average was 75.50 mL/min and after 5x chemotherapy the average was 73.24 mL/min. There was a significant difference in creatinine clearance values for DLBCL lymphoma patients before and after administration of R-CHOP (p=0.018).

Conclusion : Administration of R-CHOP chemotherapy has a significant effect on the creatinine clearance value of DLBCL lymphoma patients.

Keywords : Creatinine clearance; Diffuse large B-cell lymphoma; R-CHOP

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (LNH), accounting for approximately 30–40% of LNH cases.[1] First-line therapy for DLBCL is a combination regimen of Rituximab, Cyclophosphamide, Hydroxydoxorubicin, Vincristine (Oncovin), and Prednisone (R-CHOP).[2]

Previous research stated that rituximab could cause acute kidney injury (AKI). Rituximab has been associated with electrolyte imbalance and AKI in patients with high circulating tumor cells (>25,000/mm^3) or advanced tumor conditions. This generally occurs within 12–24 hours after the first dose and is thought to be caused by acute tumor lysis syndrome (ATLS).[3] Cyclophosphamide as one of the chemotherapy regimens for DLBCL is also known to have nephrotoxic properties. Cyclophosphamide in long-term use has the side effect of inflammation and damage to the structure of kidney tissue.[4] Hydroxydoxorubicin toxicity affects various organs including the kidneys. Numerous studies have shown that hydroxydoxorubicin-induced toxicity is caused by oxidative stress, which results in oxidation and cross-linking of thiol groups as well as peroxidation of cell membrane lipids.[5] Vincristine (Oncovin) is known to contribute to drug-induced thrombotic microangiopathy (DITMA) through immune system-mediated mechanisms and toxicity. Vincristine is one of the common chemotherapeutic agents responsible for DITMA.[6] However, prednisone (corticosteroid) is known to be one of the R-CHOP therapy regimens but is also used in the treatment of acute kidney injury (AKI), more specifically acute interstitial nephritis (AIN), namely drug-induced AKI (75%), infection (5–10%) or autoimmune (15–20%).[7]

AKI is a common but significant complication in cancer patients. AKI is often caused by a combination of conditions including tumor lysis syndrome (TLS), urinary tract obstruction, use of nephrotoxic drugs, and sepsis. Patients with poor kidney function are less likely to receive optimal care. AKI became an important risk factor for all-cause mortality in all cancer patients in a dose-dependent manner.[8] Two recent studies described an overall one-year incidence of AKI in cancer patients between 11–20%, with higher risks in patients with hematological cancers. Some studies have noted much higher rates of AKI (60%),but are biased with a larger number of critically ill patients with hematological malignancies.[9] Research related to the effects of R-CHOP chemotherapy on the evaluation of kidney function with increasing frequency of chemotherapy in DLBCL patients has never been conducted in Indonesia. This study aims to analyze the effect of R-CHOP chemotherapy on creatinine clearance values in DLBCL lymphoma patients.

METHODS

Analytical observational study with a retrospective design involved 38 patients diagnosed with DLBCL who underwent R-CHOP chemotherapy at RSUP Dr. Kariadi Semarang between January 2022 to January 2023. The research sample used medical record data obtained using the whole sampling method, namely taking all patients who met the inclusion criteria and did not have exclusion criteria during the period January 2022 to January 2023 to be used as research subjects. Inclusion criteria were 1) patients diagnosed with Diffuse Large B-cell Lymphoma (DLBCL), 2) patients receiving R-CHOP therapy, and 3) complete medical record data. Exclusion criteria were 1) patients with a history of amputation, 2) patients with hypothyroidism/hyperthyroidism, and 3) patients who were pregnant. The independent variable in this study was the frequency of chemotherapy. The dependent variables of the study were serum creatinine levels and creatinine clearance which were measured in 4 phases, namely before, post 3x-, post 4x- and post 5x- R-CHOP chemotherapy. Creatinine clearance evaluation is used as an indicator of kidney function. Calculations are performed using the Cockcroft-Gault formula using baseline data of age, weight, serum creatinine levels and gender. Patients are said to have AKI if the creatinine clearance value is <60 mL/minute/1.73m^2 based on The Kidney Disease Improving Global Outcomes (KDIGO) criteria. Data analysis was carried out using the statistical application SPSS Edition 29. Analysis was carried out using the Friedman because the analysis was conducted on >2 groups, the data was on a numeric scale, the data distribution was not normal, and the evaluation was pre-post. Results are significant if p<0.05.

The research has obtained ethical permission from the Health Research Ethics Committee RSUP Dr. Kariadi Semarang with no. 1461/EC/KEPK-RSDK/2023 and Research Permit Letter from RSUP Dr. Kariadi Semarang with no. DP.04.01/I.II/7592/2023

RESULTS

The assessment was carried out on 38 patients diagnosed with DLBCL who underwent R-CHOP chemotherapy at RSUP Dr. Kariadi Semarang, the following results were obtained.

DLBCL patients at RSUP Dr. Kariadi Semarang is dominated by women (55.3%) with an average age of 56 years. The most reported stages of DLBCL were stage II (60.5%) and stage IV (21.1%). The serum creatinine values before chemotherapy, post-3x-, post-4x- and post-5x- were 1 mg/dL, 0.8 mg/dL, 0.92 mg/dL and 0.92 mg/dL. Evaluation of comorbidities found that 2 patients (5.3%) had diabetes mellitus, and 7 patients (18.4%) had hypertension.

TABLE 1
Demographics of DLBCL patients

Variable	n (%)	Mean ± SD	Median (min–max)
Gender		–	–
Male	17 (44.7)		
Female	21 (55.3)		
Age	–	–	58 (21–77)
DLBCL Stage		–	–
Stage I	7 (18.4)		
Stage II	23 (60.5)		
Stage III	0 (0)		
Stage IV	8 (21.1)		
Creatinine serum	–		
Before chemotherapy		–	1 (0.6-1.7)
After 3x chemotherapy		–	0.8 (0.4-1.7)
After 4x chemotherapy		0.92 ± 0.289	–
After 5x chemotherapy		0.92 ± 0.247	–
Diabetes mellitus		–	–
Yes	2 (5.3)		
No	36 (94.7)		
Hypertension		–	–
Yes	7 (18.4)		
No	31 (81.6)		

TABLE 2
Creatinine clearance of DLBCL patients

Variable	Mean ± SD	Median (min – max)	*P*
Creatinine clearance value			0.018
Before chemotherapy	68.98 ± 23.440	–	
After 3x chemotherapy	–	73.12 (32.22 – 202.81)	
After 4x chemotherapy	–	66.87 (34.24 – 198.33)	
After 5x chemotherapy	–	67.33 (36.52 – 198.33)	

Friedman's test; significant p<0.05

Evaluation of creatinine clearance values before chemotherapy, after 3x-, after 4x- and after 5x- showed a value of 68.98 mL/min/1.73m2, 73.12 mL/min/1.73m^2, 66.87 mL/min/1.73m^2 and 67.33 mL/min/1.73m^2. Analysis found that there was a significant difference (p=0.018) in creatinine clearance values between R-CHOP chemotherapy phases.

Evaluation of creatinine clearance status showed that before chemotherapy most patients had creatinine clearance values > 60 mL/min (60.5%). After 3x-, 4x- and

TABLE 3
Creatinine clearance status of DLBCL patients

Variable	n (%)
Creatinine clearance before chemotherapy	
<60 mL/min/1.73m^2	15 (39.5)
≥60 mL/min/1.73m^2	23 (60.5)
Creatinine clearance after 3x chemotherapy	
<60 mL/min/1.73m^2	8 (21.1)
≥60 mL/min/1.73m^2	30 (78.9)
Creatinine clearance after 4x chemotherapy	
<60 mL/min/1.73m^2	12 (31.6)
≥60 mL/min/1.73m^2	26 (68.4)
Creatinine clearance after 5x chemotherapy	
<60 mL/min/1.73m^2	13 (34.2)
≥60 mL/min/1.73m^2	25 (65.8)

5x- chemotherapy, there was an increase in the number of patients who experienced a decrease in creatinine clearance values, where patients who had creatinine clearance values <60 mL/min were 21.1%, 31.6% and 34.2%.

DISCUSSION

In this study, the research subjects had a median value of 58 years where the youngest was 21 years and the oldest was 77 years. Research assessing the influence of age on the final clinical course of DLBCL patients, found that from an assessment of 7166 patients, the average patient age was 68 years (60–79 years). A total of 2,343 subjects received R-CHOP therapy. Subjects aged 60–69 years have a 3.38x (CI95%= 2.65–4.11) higher risk of death from DLBCL than subjects aged 20–29 years.[10] Another study assessing age as a predictor of late clinical outcome in DLBCL patients in Sweden found that from an assessment of 1169 adult patients the median age value was 64.6 years.[11] The results of this study showed that the average age of DLBCL patients when the diagnosis was made was 51.83 years, where the youngest age was 22 years and the oldest age was 77 years.[12]

DLBCL is the most common B-cell non-Hodgkin's lymphoma (LNH).[13] The incidence rate increases with increasing age and the incidence is most often found in patients aged >65 years. DLBCL usually occurs in patients with comorbid diseases or very advanced age (≥80 years). Many of these patients receive R-CHOP type chemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) or R-CHOP-like therapy based on the patient's general condition.[14]

In this study it was found that most patients were women, this is thought to be due to the high mortality rate in male patients, so that most patients who received complete chemotherapy treatment until the end were women. Estrogen is known to play a role in the inhibition of nuclear factor kappa B (NF-κB). NF-κB regulates the transcription of interferon regulatory factor 4 (IRF4). IRF4 is involved in B and T cell differentiation and is overexpressed in B cell malignancies resulting from NF-κB hyperactivation.[15] Thus, the combination of IRF4 polymorphisms and estrogen deficiency can cause men to be more susceptible to immune cell malignancies, one of which is DLBCL. Estrogen is also known to increase the expression of B-cell lymphoma-extra-large (Bcl-XL), a well-known anti-apoptotic protein, compared with testosterone.[16]

The cancer stages most reported in this study were stage II and stage IV. Research finds that most DLBCL patients have stages IV and II. Subjects with stage IV DLBCL had a 1.37x (95% CI=1.19–1.54) higher risk of death from DLBCL than subjects with stage I DLBCL.[10] Another study reported that the most common stage of DLBCL was stage I-II (61.1%).[12]

There was a significant difference in creatinine clearance values at all stages of chemotherapy (p=0.018). Increased frequency of R-CHOP chemotherapy is associated with increased creatinine clearance in DLBCL patients. Before R-CHOP chemotherapy, most study subjects (60.5%) had good creatinine clearance values (>60 mL/minute). Administration of R-CHOP chemotherapy after cycles 1, 3, 4 and 5 showed an increase

in creatinine clearance in 5.8% of subjects, 18.4% of subjects, 7.9% of subjects and 5.3% of subjects, respectively.

A study assessing the effects of minimal renal toxicity in DLBCL patients receiving R-DHAP chemotherapy found that a decrease in creatinine clearance was observed after each cycle of R-DHAP. A statistically significant decrease in GFR was obtained after the third and fourth cycles of R-DHAP administration.[17] Research that has been conducted reports the incidence of acute kidney injury in DLBCL patients who received the R-CHOP regimen.[18] Evaluation of 653 newly diagnosed DLBCL patients who received R-CHOP regimen therapy found that 133 (20.3%) patients had creatinine clearance levels of less than 60 mL/min. Patients with low creatinine clearance levels were generally older, had advanced stages of DLBCL, extranodal involvement, high lactate dehydrogenase (LDH) levels, and a high proportion of nongerminal cell (GC) subtypes, which are indicators of poor prognosis. Therefore, patients with lower creatinine clearance levels showed worse PFS (5-year PFS 74.2% vs. 80.8%, $p = 0.13$) and OS (5-year OS 77.1% vs. 86.9%, $p = 0.013$).[19] Gamez DLG, *et al* who assessed the incidence of secondary CKD due to chemotherapy in NHL patients found that from the evaluation of 16 NHL patients there were 4 different types of chemotherapy were administered, R-CHOP was administered to 10 patients (62.5%), ERCHOP to 3 patients (18.75%), ESHAP to 1 patient (6.25%) and Metrotexate + Rituximab to 2 patients (12.5%). Of the 16 patients analyzed, 7 had AKI (43.75%), 6 of them received R-CHOP, of which 4 developed CKD (52.14%).[20]

Rituximab is a chimeric anti-CD20 monoclonal antibody used for various cases of LNH. Rituximab is administered as monotherapy but can also be used in conjunction with other regimens including CHOP. The CHOP regimen is used as standard first-line treatment in the management of NHL. The standard CHOP regimen consists of day 1 VCR 1.4 mg/m^2, day 1 DXR 50 mg/m^2, day 1 CPA 750 mg/m^2, and days 1–5 PSL 100 mg/body. VCR is a vinca alkaloid that is primarily metabolized in the liver. VCR and its metabolites are excreted 69% in the feces and 12% in the urine 72 hours after administration. The anthracycline DXR and its major metabolite doxorubicinol are largely eliminated by the kidneys. CPA is an alkylating agent that undergoes biotransformation into active metabolites in the liver. The half-life of CPA in plasma varies greatly between individuals, and ranges from 1.8 to 9.2 hours. Approximately 30–60% of CPA is eliminated by the kidneys in the initial form of the drug or as its metabolite products.[21]

Patients with low creatinine clearance levels are generally older, have advanced DLBCL, extranodal disease, high lactate dehydrogenase (LDH) levels, and a high proportion of non-germ cell (GC) subtypes, which are indicators of poor prognosis.[19]

The limitation of this study was only discusses DLBCL patients within the scope of ENT-KL science but does not include DLBCL patients in other scientific scopes, such as Internal Medicine.

CONCLUSION

Administration of R-CHOP chemotherapy has a significant effect on the creatinine clearance value of DLBCL lymphoma patients. The use of R-CHOP chemotherapy in DLBCL patients is safe for the patient's kidney function. However, evaluation of kidney function should be carried out continuously to monitor kidney function as optimally as possible because decreased kidney function requires adjustment of the dose of R-CHOP chemotherapy, thus limiting the optimal benefits obtained by the patient.

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