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Original Research Article

Lymphocyte-monocyte ratio as predictive factors for huvos scores in osteosarcoma extremities treated by neoadjuvan chemotherapy (cisplatin and doxorubicin)

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ABSTRACT

Background: Chemotherapy is a vital treatment in osteosarcoma but it's responses are difficult to predict, and there are still no biomarkers that can estimate the prognosis of chemotherapy. Lymphocytes and monocytes are key immune cells which are examined on complete blood count test before chemotherapy and often associated with prognosis of various malignancies. Low lymphocyte-monocyte ratio (LMR) are associated with poor prognostics in some cancers.
Methods: This study is cross-sectional retrospective analytics that was conducted at Sanglah Hospital from June to August 2018. The research subject was medical records of intramedullary conventional osteosarcoma patients which fulfil inclusion and exclusion criteria. In this study, LMR as independent variable and Huvos score as dependent variable.
Results: The result in this study showed positive correlation between LMR before neoadjuvan Chemotherapy and Huvos score ($r=0.500$) with $p<0.05$.
Conclusions: A positive correlation was found between LMR and Huvos scores. Low LMR before neoadjuvan chemotheraphy (<2.81) were correlated with low huvos scores (grade I and II).

Keywords: Osteosarcoma, Lymphocyte-monocyte ratio, Huvos score

INTRODUCTION

Osteosarcoma, also called osteogenic sarcoma, is a malignant neoplasm originating from poorly differentiated cells in the metaphysical area of long bones in children. A poor prognosis in osteosarcoma is characterized by an 80% mortality rate after 5 years at diagnosis.[1] The incidence of osteosarcoma in the entire population is approximately 4-5 for every 1 million population. It is higher in young adults 8-11 every 1 million population at the age of 15-19 years.[2] Lately osteosarcoma has a better prognosis, due to better diagnosis and staging procedures. Treatment modality of osteosarcoma, can be divided into two parts, namely chemotherapy and surgery.[3] Chemotherapy is a very vital treatment and the standard regimen used is preoperative and postoperative chemotherapy. To assess the response of a preoperative chemotherapy, it can be done by performing a histological evaluation of the resected specimen. Based on the percentage of viable tumor cells postchemotherapy, the responses can be categorized as Huvos scores.[4,5]

The response of chemotherapy is difficult to predict, until now there are no biomarkers that can estimate the prognosis of chemotherapy, so that clinicians often have difficulty answering questions posed by patients or families about the possibility of successful chemotherapy. Neoadjuvant chemotherapy followed by definitive surgery is standard therapy for osteosarcoma patients. However, the lack of an efficient method for predicting therapeutic response, limits the clinical evaluation of a patient's eligibility for neoadjuvan chemotherapy.[6] In the cancer microenvironment an inflammatory process occurs as a form of the body's immune response against the growth

and development of cancer cells; immune system known as immune surveillance. Several studies have shown that inflammation has a significant role in various stages of growth of cancer cells such as in the phase of initiation, promotion, conversion towards malignancy, invasion, migration, and metastasis. Lymphocyte and monocyte cells are part of leukocyte cells which are often examined during complete blood count tests and are routine procedures that are performed before being given neoadjuvan chemotherapy. Low lymphocyte-monocyte ratios are known to be associated with poor prognostics in some cancers.[6] These studies indicate that, the lymphocytes monocytes ratio can be used as a prognostic indicator to assess chemotherapy response for osteosarcoma patient.

METHODS

This study is cross-sectional retrospective analytics that was conducted at Sanglah Hospital from June to August 2018. Clinical, laboratory and radiological data were obtained from patient medical records and histopathological examination (Huvos score) was carried out at the Pathology anatomy section.

Inclusion criteria

The research subject are medical record of intramedullary conventional Osteosarcoma patient that fulfil inclusion criteria which includes: diagnosed osteosarcoma based on histopathological results, have never received any systemic chemotherapy before routine haematological examination, getting first-line neoadjuvant chemotherapy cisplatin and doxorubicin and complete data.

Exclusion criteria

Exclusion criteria for the study was as follows: incomplete clinical and histopathological data, having an infectious disease, having hematologic malignancies-myeloproliferative, lymphoproliferative and immunoproliferative diseases, inflammatory diseases and autoimmune diseases- Systemic lupus erythematosus (SLE), rhematoid arthritis. In This study, LMR as independent variable and Huvos score as dependent variable.

RESULTS

Descriptive data analysis aims to obtain a clearer picture of the distribution of each research variable. The total number of research subjects is 23. From the descriptive statistical analysis (Table 1), we can identify the characteristics of the study subject, where the average age of subject involved in the study was 23.86 years with more men than women with 13 people (56.5%), most of the osteosarcomas found in the distal femur and proximal tibia respectively 7 people (30.4%) followed by proximal humerus, proximal femur, distal radius and distal tibia.

Table 1: Characteristic of research samples.

Characteristics	Total (n=23)
Gender	
Male	56.5% (13)
Female	43.5% (10)
Age	23.8696±10.23054
Tumor location	
Distal femur	30.4% (7)
Proximal tibia	30.4% (7)
Proximal humerus	17.4% (4)
Proximal femur	13% (3)
Distal radius	4.3% (1)
Distal tibia	4.3% (1)
Pathological fracture	
Yes	26.1% (6)
No	73.9% (17)
Ratio lymphosit monosit	2.2583±1.47152
Alkaline phospatase level	274.3913±288.120
Lactate dehydrogenase level	617.6087±327.104
Score Huvos	
Necrosis	
<50%	56.6%
50-90%	30.4%
90-99%	8.7%
100%	4.3%

In this study a test was conducted to determine the relationship between the ratio of lymphocytes and monocytes before neoadjuvant chemotherapy with Huvos scores. To find out the lymphocyte and monocyte ratio cut-off points, an Receiver-operating characteristic (ROC) curve analysis was carried out. From the Area under the curve (AUC) (Table 2) and ROC curve of the lymphocyte and monocyte ratio (figure 1), AUC of 0.900 was obtained with p=0.028 (95% Confidence interval (CI): 0.772-1,000). Statistically the AUC value of 90% is good. Cut of point to determine the ratio of low and high monocyte lymphocyte ratio is determined by Receiver operating characteristic procedure (Table 3). From the sensitivity and specificity tables and curves (figure 2), the intersection point between the sensitivity and specificity of the lymphocytes and monocytes ratio is at 2.81. The lymphocyte and monocyte ratio below 2.81 is categorized as a low, while those above 2.81 are categorized as high (Table 4).

With predetermined cut of points, lymphocytes and monocytes ratio are categorized as low lymphocyte monocyte ratio (low LMR) and high lymphocyte monocyte ratio (high LMR). It was found that low LMR was found in the amount of 17 (73.9%) people sampled. We described the relationship between the lymphocytes and monocytes ratio to the Huvos score in Osteosarcoma patients at Sanglah General Hospital by using cross tabulation (Table 5) and by using analysis with gamma correlation and somers'd (Table 6). In this study, researchers considered the lymphocytes monocyte ratio as independent variables, while Huvos scores as dependent

variables, then the value used is the test results of the third row somer's test, the correlation is 0.500 which indicates that the correlation is of moderate strength. p value is 0.032 which means there is a significant correlation between the two variables tested.

Table 2: Area under the curve (AUC).

Area	Asymptotic sig.[b]	Asymptotic 95% CI	
		Lower bound	Upper bound
0.900	0.028	0.772	1.000

Table 3: Sensitivity and specificity receiver operating characteristic.

Positive if greater than or equal to[a]	Sensitivity	Specificity
-0.1000	1.000	0
0.9500	1.000	0.05
1.0350	1.000	0.1
1.0750	1.000	0.15
1.0850	1.000	0.2
1.0950	1.000	0.25
1.1850	1.000	0.3
1.2750	1.000	0.35
1.3400	1.000	0.4
1.4900	1.000	0.5
1.6400	1.000	0.55
1.7900	1.000	0.6
1.8850	1.000	0.65
1.8950	1.000	0.7
1.9500	1.000	0.75
2.0500	1.000	0.8
2.8150	1.000	0.85
3.9000	0.667	0.85
4.2750	0.667	0.9
4.3900	0.333	0.9
4.9000	0.333	0.95
5.3600	0.000	0.95
6.4200	0.000	1

Table 4: Distribution of research subjects based on lymphocyte monocyte ratio.

LMR	Frequency	Percentage
LMR low (< 2.81)	17	73.9
LMR high (>2.81)	6	26.1

Table 5: Cross tabulation between the lymphocyte-monocyte ratio cut-off and huvos score.

		Score huvos		Total
	LMR	Grade 1 dan grade 2	Grade 3 dan grade 4	
Cut of LMR	**<2.81**	17	0	17
	>2.81	3	3	6
Total		20	3	23

Table 6: Correlation between LMR and huvos score.

Somer's d	Value	Approximate significance
Symmetric	0.630	0.032
LMR high dan low dependent	0.850	0.032
Huvos dependent	0.500	0.032

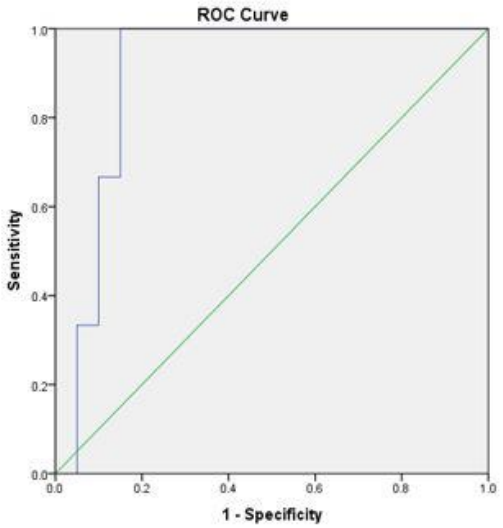

Figure 1: ROC curve lymphocyte-monocyte ratio.

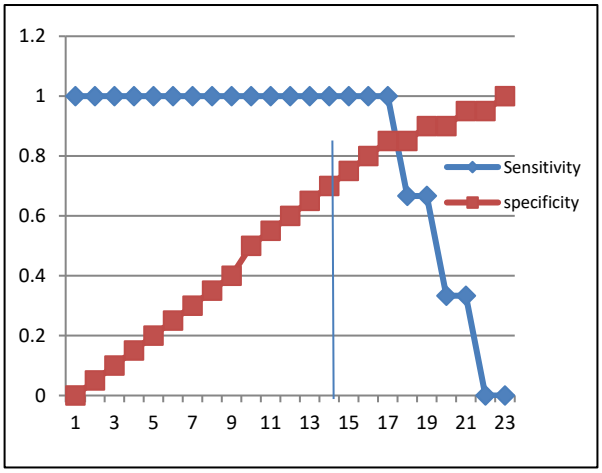

Figure 2: Sensitivity and specificity curve of lymphocyte and monocyte ratio.

DISCUSSION

The study involved 23 osteosarcoma patients from the Orthopaedic Department of Sanglah General Hospital, Denpasar. Subjects were patients whose data obtained from 2015 to 2018. The average age of the study patients was 23.86. This is consistent with the study of Ottaviani which states that the high incidence of osteosarcoma at the age of 10-20 years and 60 years.[7]

The lymphocytes monocyte ratio (LMR) is an inflammatory marker that was recently introduced and used in many studies, where LMR is simple and low cost.[8] The value of LMR has a predictive value on the prognosis, severity and mortality in many cases of malignancy including blood disorders and solid tumors. Low preoperative LMR values are associated with poor prognosis in osteosarcoma patients.[9]

According to Chen et al, low LMR before chemotherapy is associated with a poor prognosis in cervical cancer.[10] While Jiang et al use LMR before chemotherapy as a free prognostic factor in patients with metastatic nasopharyngeal carcinoma.[11] Zhang et al found that preoperative LMR was a better prognostic factor in patients with bladder cancer who underwent radical cystectomy.[8]

According to Liu et al, there are only a few data that show LMR associated with the prognosis in osteosarcoma. Research by Liu et al was the first study to try to evaluate the effect of LMR on the prognosis of 327 osteosarcoma patients and develop a predictive model to improve predictive accuracy for survival of 3 years and 5 years.[9]

In this study, the lymphocytes monocyte ratio is as independent variables and Huvos scores were associated as dependent variables acting as response parameters for neoadjuvant chemotherapy, then the Somer's correlation test results were obtained with r=0.500 indicating that there was a moderate correlation. The p value is 0.032 which means that there is a significant correlation between the ratio of monocyte lymphocytes and Huvos scores.

CONCLUSION

From the data analysis carried out in this study, it can be obtained that there is a moderate strength relationship between the ratio of lymphocyte-monocytes before therapy with chemotherapy response in patients with osteosarcoma (Huvos Score).

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Ethical approval: The study was approved by the Institutional Ethics Committee

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