Association between laboratory markers and oncological outcomes in patients with osteosarcoma – A review of osteosarcoma treatment in Indonesia

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Abstract

Background: Treatment of osteosarcoma requires multi-disciplinary team work and a rigorous follow-up schedule to achieve best oncological and functional outcomes. However, standard treatment and routine image study may not be available for all Indonesian patients because of complex geographic reason in Indonesian archipelago. Therefore, we aimed to review treatment outcome of osteosarcoma in Indonesia and validate potential laboratory markers associated with oncological outcomes.

Materials and Methods: From January 2015 to August 2016, we retrospectively reviewed 57 patients with osteosarcoma who had received treatment in Dr. Cipto Mangunkusumo Hospital (RSCM), Jakarta, Indonesia. Association between laboratory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), alkaline phosphatase (ALP) and oncological outcomes including mortality and distant metastasis have been validated.

Results: Our results showed that a combination of neoadjuvant chemotherapy, tumor resection and adjuvant chemotherapy would lead to the best oncological and functional outcome. ESR, CRP LDH and ALP level decreased after surgery and chemotherapy. Lower level of ESR and CRP were not associated with less distant metastasis and less mortality. On the other hand, the elevated LDH was correlated with higher mortality ($P < 0.01$), whereas elevated ALP was also correlated with a higher risk of distal metastasis ($P = 0.044$).

Conclusions: Patients who had been properly treated with neoadjuvant chemotherapy, tumor resection and adjuvant chemotherapy had the best oncological and functional outcomes. LDH and ALP might be useful laboratory markers to predict oncological outcome.

Keywords: Alkaline phosphatase, C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, osteosarcoma

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INTRODUCTION

Osteosarcoma is a primary bone malignancy that characterized by the formation of immature bone or osteoid tissue by the tumor cells. The incidence of osteosarcoma reach 2–3 per/million population. Conventional osteosarcoma, a high degree of malignancy, contributing for 80%–90% of all cases of osteosarcoma found. In Cipto Mangunkusumo Hospital (CMH), we found 219 cases of osteosarcoma as a common bone malignancy from 1995 to 2007.

Laboratory examination of osteosarcoma includes erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) examination. Beside laboratory examination, there were other examinations previously performed before the clinicopathological conference including radiological and histopathology examinations. Then, the diagnosis of osteosarcoma was confirmed in a clinicopathological conference involving orthopedics oncologists, musculoskeletal radiologist, anatomic pathologist, medical oncology, and hematologist.

Primary bone malignancy therapy has developed rapidly in recent decades. Now, chemotherapy is known as a vital treatment for osteosarcoma. Chemotherapy decrease and delay the incidence of metastasis. Multimodality therapy which consists of neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy has resulted in better survival rate, reaching 75%–80%. The progress in the treatments requires a monitoring of a local recurrence or metastasis. Chemotherapy, tumor size, the location of the tumor, and laboratory examination such as ESR, CRP, LDH, and ALP were employed as the parameters.

Until recently, there has been no related study conducted in CMH. The assessment of laboratory values in this study can be applied to determine the effect of various treatment of osteosarcoma to ESR, CRP, LDH, and ALP and its relationship to the oncology outcomes.

SUBJECTS AND METHODS

The target population of this study was the patients with osteosarcoma who underwent neoadjuvant and adjuvant therapy in CMH from January 2015 to August 2016. A sampling was obtained sequentially to all populations that met the inclusion criteria. A sampling method used in this study was a descriptive-proportions method. The prevalence of the sampling was 4.83% compared with the overall prevalence of malignancy. Based on the descriptive-proportions method, the rate of the subjects were 17.66 or 18 samples. A total of 20 subjects of each group of actions were gained from 10% drop out rate of the whole subjects.

Data analysis was conducted by applying SPSS v. 23 Windows® (SPSS Inc., Chicago, Illinois, USA) with descriptive analysis and test normality of data. A cross-tabulation of frequency, with the Chi-Square test, was applied to determine the $P$ value of the categorical data. Numerical data included mean and median. The difference of the mean value was analyzed by parametric test and nonparametric test. A parametric test was for a nonnormally distributed data.

The study design used in this study was descriptive analytic cross-sectional study. The study took place from January 2015 to August 2016, while the stage of processing, analysis, and reporting was conducted in September 2016. Data collected were grouped based on the treatment period [Figure 1]. Patients considered as inclusions criteria...
received a combination of neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy.

The inclusion criteria consisted of osteosarcoma patients who were treated at CMH between January 2015 and August 2016; patients who underwent neoadjuvant and adjuvant therapy at CMH from January 2015 to August 2016, and patients received a control for 1 month at the stage of posttherapy. The duration of a month control was used to determine how many patients who underwent in a treatment and patients who had conducted a laboratory test for ESR, CRP, ALP, and LDH.

The exclusion criteria consisted of patients with osteosarcoma from other hospitals at the similar period (January 2015–August 2016) who received neoadjuvant and adjuvant therapy once; patients who had laboratory tests outside CMH. There were five group divisions of the patients including Group 1 (chemotherapy [neoadjuvant and adjuvant] with surgery), Group 2 (surgery with adjuvant), Group 3 (neoadjuvant), Group 4 (surgery), and Group 5 (neoadjuvant with surgery).

**Ethical approval**

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the institute. Informed written consent was obtained from all patients prior to their enrollment in this study.

**RESULTS**

**Demographic characteristics and study population**

Based on the inclusion and exclusion criteria, the total of the study population was total 57 patients with osteosarcoma. Patients received a combination of neoadjuvant chemotherapy, surgery, and adjuvant chemotherapy. Then, the patients were stratified based on the treatment adopted during therapy [Table 1].

**Categorical analysis of laboratory variable with mortality and metastasis**

This analysis used to categorize the laboratory variables and associate it with the possibility of mortality and metastasis in patients.

**Laboratory variable versus mortality**

The first group with regimen neoadjuvant chemotherapy, surgery, and adjuvant yielded there was no relation between laboratory variables with mortality. Meanwhile, a Group 2 was unable to analyze and to create association-crossable since the sample size was insufficient, only five samples.
In the third group [Table 2], it is presented that there is no a significant relation between laboratory variables with mortality. ALP post-neoadjuvant variables could not be assessed due to insufficient data to create cross tabulations.

In the fourth group, there is no significant relation between the laboratory variables with mortality. LDH variables could not be assessed due to insufficient data to make a cross-tabulation table.

**Laboratory variable versus against metastasis**

The cumulative relationship between the laboratories values and metastatic status were provided in Table 3. Based on the Fisher’s exact Test, all of the variable values had no correlated with metastasis, except for the LDH variable after surgery \( (P = 0.043) \) and the ALP after adjuvant chemotherapy \( (P = 0.044) \).

A cross-tabulation table for assessment was applied to observe a cumulative relation between laboratory variables categories with metastasis. In Table 4, the LDH of postsurgery was high (category 2). This result proved that LDH of postsurgery had a relation with the incidence of nonmetastasis cases.

Based on the cross-tabulation table, it was found that ALP postadjuvant was associated with an incidence of metastasis [Table 5]. In addition, there was no relation between the actions of Group 1 with metastasis [Table 5], and there was no relation between the action categories 2 with metastasis in patients [Table 5].

There was no a significant difference between the treatment Group 3 with the status of metastasis in this study [Table 5]. In line with the result, the statuses of metastasis had no relation with the treatment Group 4 [Table 5].

**DISCUSSION**

In this study, we found the decrease of ESR mean from the pretreatment group compared to the ESR mean on the group after neoadjuvant, postsurgery, and postadjuvant. There was no significant difference found in both groups. The mean value of ESR on each treatment group had no relation with the status of metastasis and the mortality rate of patients. Theoretically, this result was different from the study conducted by Hannisdal et al.\[10\] which stated that the ESR has increased in 16 patients with osteosarcoma and Ewing osteosarcoma patients with relapsing phase.

Statistical analysis showed ESR future relapses significantly different from the ESR at the time of remission. The most striking difference was in the group with Ewing’s sarcoma (ESR median remission phase \( = 7 \) mm/h, the ESR median relapse phase \( = 60 \) mm/h; \( P < 0.0001 \)), therefore, Hannisdal et al.\[10\] concluded that ESR can be used as an indicator of disease activity. Another related study conducted by Ilić et al.\[9\] in proved that the ESR is one of the prognostic factors in osteosarcoma and Ewing sarcoma.

ESR tended to be elevated in the women patients, pregnant, infections, and malignancies. In malignancy, an elevated ESR was found along with the course of their illness. Ilić et al.\[9\] found that ESR increased for \( >12 \) mm/h in pediatric patients with sarcoma. Furthermore, the success rate of life in patients with osteosarcoma was different from the patients with normal ESR \( (P = 0.014) \) as well as from the patients with high ESR.

ESR was influenced by the concentration of immunoglobulins and acute phase proteins (fibrinogen, CRP, alpha-1 antitrypsin, and haptoglobin). According
to this occurrence, ESR was applied as an indicator of sensitive inflammation and tissue damage that is sensitive but not specific for osteosarcoma.

The relation between inflammation and cancer had been extensively studied since the study had first reported by Virchow.\textsuperscript{11} Cancer cells in the tumor tissue were embedded with a persistent inflammatory condition, namely, microenvironment tumor.\textsuperscript{12,13} By the similarity, role of CRP serum in other malignancies, high serum levels of CRP was associated with poor prognosis in patients with soft-tissue sarcoma.\textsuperscript{14,15} Yi \textit{et al.}\textsuperscript{16} through their literature searches found that the increase in serum CRP had an adverse effect on the overall survival of patients with osteosarcoma ($n = 397$ in two studies; relative risk 0.35; $P = 0.002$ 95% confidence interval).\textsuperscript{16} In this study, we found there was no significant changes of CRP value before and after treatment. The mean value of CRP in each treatment group had no relation to the patient’s status of metastasis and mortality.

The relation between CRP and cancer was causal due to some conditions which increased the value of CRP without increasing the risk of cancer.\textsuperscript{17,18} Some clinical findings indicated that CRP significantly increased in cancer patients, despite its direct relation was still unknown. The increase of CRP value was caused by inflammation in the body or vice versa.

LDH functioned to describe systemic cancer activity and prognostic significance in a variety of malignancies description.\textsuperscript{19} This study showed the pretreatment LDH levels had mean of 1054.72 U/L (very high) and mean postsurgery 467.48 U/L (high). Moreover, the results of this study showed high LDH category (300–1000 U/L) were not associated with the incidence of metastasis. The prognostic variables of LDH were increased significantly.

\begin{table}[h]
\centering
\caption{The relationship between laboratory variables of each group with mortality}
\begin{tabular}{|c|c|c|c|c|}
\hline
Variable of laboratory value & Pretreatment & Postneoadjuvant & Postsurgery & Postadjuvant \\
\hline
\hline
\textbf{Group 1} & & & & \\
ESR & 1.000 & 1.000 & 1.000 & 1.000 \\
CRP & 1.000 & 1.000 & 0.467 & 1.000 \\
LDH & 1.000 & 1.000 & 0.333 & 1.000 \\
ALP & 0.267 & 1.000 & 1.000 & 1.000 \\
\hline
\textbf{Group 3} & & & & \\
ESR & 0.532 & 0.748 & - & - \\
CRP & 1.000 & 0.385 & - & - \\
LDH & 0.52 & 1.000 & - & - \\
ALP & 1.000 & N/A & - & - \\
\hline
\textbf{Group 4} & & & & \\
ESR & 0.644 & - & 0.200 & - \\
CRP & 1.000 & - & 0.467 & - \\
LDH & 0.067 & - & N/A & - \\
ALP & 1.000 & - & 0.533 & - \\
\hline
\textbf{Without treatment} & & & & \\
ESR & 0.545 & - & - & - \\
CRP & 0.182 & - & - & - \\
LDH & 1.000 & - & - & - \\
ALP & 0.545 & - & - & - \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{The cumulative relation between laboratory variables categories with metastasis}
\begin{tabular}{|c|c|c|c|c|}
\hline
Variable of laboratory value & Pretreatment & Postneoadjuvant & Postsurgery & Postadjuvant \\
\hline
\hline
\textbf{ESR} & 1.000 & 0.626 & 0.085 & 0.071 \\
\textbf{CRP} & 0.626 & 0.485 & 0.455 & 0.146 \\
\textbf{LDH} & 0.673 & 1.000 & 0.043 & 0.483 \\
\textbf{ALP} & 0.909 & 0.567 & 0.399 & 0.044 \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{The relationship between cumulative lactate dehydrogenase postsurgery and alkaline phosphatase post-adjuvant with the incidence of metastasis}
\begin{tabular}{|c|c|c|}
\hline
Variables & Metastasis & No metastasis \\
\hline
\textbf{LDH} & & \\
Normal (<300) & 3 & 2 \\
High (300-1000) & 5 & 20 \\
Very high (>1000) & 1 & 0 \\
\textbf{ALP} & & \\
Normal (<98) & 0 & 7 \\
High (98-500) & 7 & 6 \\
\hline
\end{tabular}
\end{table}
These occurrences were found in various types of pediatric tumor; however, LDH was not a specific marker. There was a relation between the increase of LDH and the expansion of the tumor and the prognosis.[18] This result was in line with other related studies that found a significant difference between the mean LDH in the postsurgical group and metastatic status. Thus, the mean value of LDH in the treatment group had no relation with mortality.

The role of ALP is to provide diagnostic information. Robinson in 1923, in his study, found an increase of ALP serum activity followed by the increase of osteoblast activity.[19] A study conducted by Meyers et al.[15] said that the value of bone ALP was higher in patients with osteosarcoma than in benign bone tumor, and there was a relation between the decline in the value of bone ALP and improved histological response.

This study found a marked change of variables ALP before the treatment with postadjuvant chemotherapy in Group 1. The previous related studies proved ALP serum values increased extensively from 40% to 80% in patients with osteosarcoma.[19] another related study which had a larger sample size found that the value of serum ALP increased as much as 40.2%–83.7%.

The relation between total serum ALP activity with clinical outcomes of osteosarcoma has been recognized for >50 years, however, it still controversial.[20]

Metastasis is the most important prognostic factors in osteosarcoma; local patients with metastatic osteosarcoma led to different results. The analysis showed that there was a relation between serum ALP values (above 98–500 U/L) with metastatic status. However, the mean value of ALP in the treatment group had no relation with mortality. In this study, ALP value test performed to the patients who came first (before the intervention), after undergoing neoadjuvant therapy, 1 month after completion of chemotherapy, and 1 month after the surgery was completed. In accordance with the study from Brammer et al.[21] the ALP must be examined twice; first at the stage of chemotherapy and the last at postchemotherapy. Both of those examinations were performed to determine a more precise prognosis.[21]

**CONCLUSIONS**

One of the major factors that affect the outcome of this study was the various clinical conditions of the patients.

This detailed study can be attributed for further treatment of the patient with osteosarcoma. Moreover, this study showed the ESR, CRP, LDH, and ALP decrement was observed after regiments of chemotherapy and surgery conducted. A complete regiment (neoadjuvant-surgery-adjuvant) has resulted in a longer lifespan of the patients.

In addition, the more complete regiment is the most excellent treatment to the patients.

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**Conflicts of interest**

There are no conflicts of interest.
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