FEBS Open Bio 5 (2015) 682–687

FEBS openbio

journal homepage: www.elsevier.com/locate/febsopenbio

Pre-operative lymphocyte-to-monocyte ratio as a predictor of overall survival in patients suffering from osteosarcoma

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ARTICLE INFO

Article history:
Received 2 July 2015
Revised 31 July 2015
Accepted 3 August 2015

Keywords:
Osteosarcoma
LMR
Prognosis
Nomogram

ABSTRACT

Inflammatory markers have been proposed to predict clinical outcomes in many types of cancers. The purpose of this study was to explore the influence of the lymphocyte-to-monocyte ratio (LMR) on clinical prognosis of patients with osteosarcoma. This study collected 327 patients who underwent surgical treatment for osteosarcoma during the period 2006–2010. LMR was calculated from pre-operative peripheral blood cells counts. The optimal cut-off value of LMR was determined based on receiver operating characteristic curve analysis. Overall survival (OS) and event free survival (EFS) was plotted using the Kaplan–Meier method and evaluated by the log-rank test. A predictive model was established to predict clinical prognosis for OS, and the predictive accuracy of this model was determined by concordance index (*c*-index). Our results showed that young age, elevated alkaline phosphatase, metastasis at diagnosis, chemotherapy, lymphocyte and monocyte counts were significantly associated with LMR. Low LMR was associated with shorter OS and EFS ($P < 0.001$), and was an independent predictor of both OS and EFS (HR = 1.72, 95% CI = 1.14–2.60, $P = 0.010$; HR = 1.89, 95% CI = 1.32–2.57, $P = 0.009$). The nomogram performed well in the prediction of overall survival in patients with osteosarcoma (*c*-index 0.630). In conclusion, low pre-operative LMR is associated with a poor prognosis in patients suffering from osteosarcoma. A prospective study is warranted for further validation of our results.

1. Introduction

Osteosarcoma is the most common primary malignant tumors of bone [1]. Epidemiological data showed that there were two peaks of incidence in osteosarcoma patients, particularly among early adolescence aged 15–19 years [2]. In recent years, patients' age with osteosarcoma is increasing [3] and patients over the age of 40 years account for 13–30% of all patients with osteosarcoma [4]. According to epidemiological data, osteosarcoma is the eighth leading cancer with an incidence of 4.4 per million, mainly occurring in adolescents and adults [5]. Despite substantial progress achieved in diagnosis and treatment for osteosarcoma in the past decades, the overall 5-year survival remains unsatisfactory for local relapse or metastasis after surgical resection of primary osteosarcoma.

The poor clinical prognosis of osteosarcoma partially results from lack of a good indicator to detect tumors at an early stage. Furthermore, the ability to predict the prognosis of a patient is indispensable for selecting the optimal treatment plan and follow-up strategies. Although prognostic indicators are the Enneking surgical criteria [6] and alkaline phosphatase, heterogeneous clinical outcomes are frequently found within the same tumor stage. Therefore, it is necessary for us to further understand the underlying mechanisms and find a dependable indicator of osteosarcoma to predict clinical outcome.

Recently, the emerging evidence revealed that the systemic inflammatory response has been reported to be an independent prognostic biomarker in various types of tumor [7,8]. Published evidence has shown a significant link between inflammatory markers and poor prognosis in several types of tumors, including thrombocytosis, leukocytosis, high neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-

Abbreviations: 95% CI, 95% confidence interval; AUC, areas under the curve; EFS, event free survival; HR, hazard risk; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PLR, platelet-to-lymphocyte ratio; ROC, receiver operating curve analysis

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http://dx.doi.org/10.1016/j.fob.2015.08.002
2211-5463/

monocyte ratio (LMR) [9–13]. However, the influence of LMR on the prognosis of osteosarcoma patient has been not reported. Herein, the purpose of this study was to estimate the influence of LMR on clinical prognosis in 327 osteosarcoma patients at post-operation.

2. Materials and methods

2.1. Patients

The Medical Ethics Committee of The First People's Hospital of Anqing approved this study. Written informed consents were obtained from all eligible patients. Medical records of all newly diagnosed osteosarcoma patients between 2006 and 2010 in The First People's Hospital of Anqing and The Second People's Hospital of Lianyungong were reviewed and retrospectively analyzed in the present study. The diagnosis of osteosarcoma was confirmed depended on histological evidence and classified on the basis of the Enneking surgical criteria [6]. The inclusion criteria were as follows: (1) no prior pre-operative anticancer treatment, such as chemotherapy, blood transfusion, and radiotherapy. (2) All patients with osteosarcoma underwent surgical resection. (3) No hematology disease, infection and hyperpyrexia. (4) Informed consents were obtained. Finally, 327 patients were enrolled in the present study. Clinical features of eligible patients were collected including age, sex, tumor location, pathological fracture, alkaline phosphatase (ALP), clinical stage, metastasis at diagnosis and post-operative chemotherapy.

2.2. Blood sample analysis

Blood samples were obtained for the measurement of lymphocyte and monocyte counts at pre-operation.

2.3. Definition and optimal cut-off value of LMR

LMR was defined as the lymphocyte counts divided by the monocyte counts. Using overall survival (OS), as end-point, the optimal cut-off value of LMR was obtained when the Youden index was maximal. Subsequently, patients with a LMR greater than the corresponding cut-off value were defined as high LMR (HLMR), and others were defined as low LMR (LLMR).

2.4. Patient follow-up

Each patient was followed up regularly until death or December 2014 at post-operation. Physical examination, laboratory tests and imageological diagnosis were performed at every visit. The follow-up period varied from 3 months to 5 years, with a median of 24 months. OS was calculated from the data of surgical resection to the data of death. Event free survival (EFS) was calculated from the data of surgical resection to the data of disease relapse, progression or tumor-related death. The date of last follow-up was used for drop-out patients.

2.5. Statistical analysis

To evaluate the sensitivity and specificity of the 5-year OS, the receiver operating characteristic (ROC) curve was applied and Youden index was estimated to determine the optimal LMR cut-off value. Comparison of categorical variables was conducted using a Chi-square test. Comparison of continuous variables was conducted using a Student's t test. Survival curves were plotted by the Kaplan–Meier method and the significance was assessed by the log-rank test. Significant predictors for OS and EFS determined by univariate analysis were evaluated by multivariate analysis using Cox's proportional hazards model. Nomogram for OS was performed by R 3.0.3 software using the package of *rms* (Institute for Statistics and Mathematics, Austria). A final model selection was performed by a backward step-down selection process, and Harrell's concordance index (c-index) was applied to evaluate the predictive accuracy. All results analyses were conducted by SPSS 17.0 software (IBM, USA). P values less than 0.05 were considered statistically significant.

3. Result

3.1. Clinicopathologic characteristics

Of 327 patients with osteosarcoma, 235 (71.9%) were male, and the mean age was 20 years (range 10–44 years; Table 1). The medians of lymphocyte counts and monocyte counts were 1220 and 340 per μL, respectively. 130 (39.8%) patients with initial metastasis and 58 (17.7%) patients with pathological fracture were recorded from newly diagnosed patients. According to Enneking surgical staging criteria, the number of stage I–II and III was 168 (51.4%) and 159 (48.6%), respectively. Pathological results suggested that 267 (81.7%) patients' osteosarcomas were located in the tibia or femur. During the follow-up period, 166 (50.8%) patients had experienced systemic chemotherapy. Among all enrolled patients, 184 (56.3%) patients died from cancer-related disease, and 217 (66.4%) patients experienced disease relapse, progression or tumor-related death.

3.2. The optimal cut-off value for LMR

The areas under the curve (AUC) for LMR were 0.665 ($P < 0.001$, Fig. 1), when the OS was employed as end-point for LMR. The optimal cut-off value was 3.43 for LMR. All patients were divided into two groups with the high group that $\geqslant$ the cut-off value (HLMR) and the low group less than the cut-off value (LLMR) on the basis of the optimal cut-off value.

3.3. The associations of LMR with clinicopathologic features

To explore associations of LMR with clinicopathologic features of osteosarcoma patients, comparisons between the high and low groups for LMR were carried out (Table 1). Our results indicated that young age, elevated ALP, metastasis at diagnosis, chemotherapy, lymphocyte counts and monocyte counts were significantly associated with LMR ($P < 0.05$). However, patients' sex, tumor location, pathological fracture and clinical stage were not found to be associated with LMR.

3.4. Prognostic factors for OS and EFS

The Kaplan–Meier curve showed that the 5-year OS rates of the LLMR group were significantly lower than those of the HLMR group ($P < 0.001$; Fig. 2A), and similar result was also observed in the 5-year EFS rates ($P < 0.001$; Fig. 2B). Subsequently, univariate analyses indicated that advanced clinical stage, metastasis at diagnosis, chemotherapy and LLMR were closely correlated with poor prognosis. Furthermore, multivariate analyses of OS and EFS were performed including age, sex and clinical variables with univariate log-rank $P < 0.05$: advanced clinical stage, metastasis at diagnosis, chemotherapy and LLMR. LLMR, advanced clinical stage and metastasis emerged as markers for shorter OS and EFS (Table 2),