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Prognostic impact of pretreatment albumin to globulin ratio in patients with diffuse large B-cell lymphoma treated with R-CHOP

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ABSTRACT

Objective: We evaluated the clinical implications of the albumin to globulin ratio (AGR) in patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP).

Methods: Data of 232 patients with DLBCL treated with first-line R-CHOP from 2004 to 2017 were reviewed retrospectively. Patients with AGR values ≥1.22 and < 1.22 were assigned to the high and low AGR groups, respectively. Treatment response, treatment-related toxicity, and survival were compared according to the AGR.

Results: The complete response rate was significantly lower in the low AGR group than in the high AGR group (59.1% vs. 81.3%; $p < 0.001$). Treatment-related mortality was also more frequent in the low AGR group than in the high AGR group (14.0% vs. 4.3%; $p = 0.009$). The low AGR group (median overall survival [OS] = 26.87 months; 95% confidence interval [CI] = 4.19–49.55) showed a significant decrease in OS compared to the high AGR group (median OS = 148.83 months; 95% CI = 76.26–221.41; $p < 0.001$). Progression-free survival (PFS) also decreased significantly in the low AGR group (median PFS = 14.29 months; 95% CI = 2.58–26.01) compared to the high AGR group (median PFS = 148.83 months; 95% CI = 76.21–221.45; $p < 0.001$). In a multivariate analysis, low AGR was an independent poor prognostic factor for OS and PFS.

Conclusions: Pretreatment AGR was useful for predicting treatment response, treatment-related toxicity, and prognosis in patients with DLBCL treated with R-CHOP. Further large prospective studies will be necessary to validate our findings.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin's lymphoma, representing about 30% of cases [1]. The introduction of rituximab (R) in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) chemotherapy, known as "R-CHOP", improves survival outcomes [2,3], and has affected the importance of formerly recognized prognostic markers [4]. In the pre-R era, the International Prognostic Index (IPI) was used to predict responses and prognoses in patients with high-risk non-Hodgkin's lymphoma [5]. However, the original IPI did not well-identify a poor prognostic group with < 50% chance for survival in the post-R era [4]. A novel prognostic marker is needed to identify patients who may benefit from different therapeutic strategies. Accumulating evidence indicates an association between systemic nutritional and inflammatory status and cancer progression [6,7]. Among the major serum proteins, changes in albumin and globulin reflect a chronic inflammatory state or malnutrition [8,9]. Albumin is characterized as a negative acute-phase protein, and its pool is modified in several inflammatory conditions [10]. Cytokines, such as interleukin-6 and tumor necrosis factor, are delivered during inflammatory responses and can inhibit the synthesis of albumin in hepatocytes [11]. Serum albumin level is a known

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prognostic marker of several solid [12–14] and hematological malignancies [15–18]. Globulin is associated with many acute-phase proteins, such as α_1-antitrypsin, α_2-macroglobulin, and haptoglobin. Several indicators during inflammation cause rapid hyperglobulinemia, which has been correlated with a poor prognosis in several malignant tumors [19,20]. The albumin to globulin ratio (AGR) is used primarily as a clinical indicator of multiple myeloma and other immunoproliferative diseases [21,22]. Moreover, the AGR has been used to anticipate clinical outcomes and prognosis in patients with non-small cell lung cancer [23], esophageal cancer [24], gastric cancer [25], and renal cell carcinoma [26].

Although an impact of systemic inflammation and cachexia on prognosis and treatment-related toxicity has been proposed for patients with DLBCL [27–30], the clinical significance of the AGR in patients with DLBCL has not been addressed. Thus, in our study, we investigated the potential clinical implications of the AGR in patients with DLBCL treated with R-CHOP. We hypothesized that a low AGR would be an independent poor prognostic factor and associated with intolerance to the R-CHOP regimen.

2. Materials and methods

2.1. Study design and patients

A retrospective study of 232 patients with newly diagnosed DLBCL between January 2004 and February 2017 at Gyeongsang National University Hospital was designed and analyzed. Patients were included if they: (1) were diagnosed with pathologically confirmed DLBCL according to World Health Organization criteria [31] by two independent hematopathologists, (2) received at least one cycle of R−CHOP as first-line therapy, and (3) had no prior history of chemotherapy or radiotherapy. Patients < 18 years of age, who were treated with frontline therapy other than the R-CHOP regimen, who had histological transformation from low-grade lymphoma to DLBCL, or who had an active infection at the time of starting R-CHOP therapy were excluded from the study. This study was approved by the Institutional Review Board of Gyeongsang National University Hospital. The requirement for informed consent was waived.

2.2. Clinical data and definitions

The following baseline demographics and clinical variables were obtained from patients' electronic medical records: gender, age at diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS), the presence of B symptoms, Ann Arbor stage, bulky disease (defined as ≥10 cm in diameter), extranodal involvement (ENI), IPI risk [5], cell-of-origin (COO) subtype by Hans' criteria [32], bone marrow (BM) examination, computed tomography (CT) scans, ^{18}F2fluoro-2-deoxyglucose-positron emission tomography (PET)/CT, and blood chemistry, including serum protein, albumin, and lactate dehydrogenase (LDH) levels. The treatment response was evaluated by a physical examination, CT scan, and PET/CT after every two or three R-CHOP cycles, and reviewed by the authors using the revised International Working Group response criteria [33]. After completing the R-CHOP therapy, the timing of the response evaluation was clinically determined. Grade ≥3 treatment-related toxicities were assessed at every visit according to the National Cancer Institute Common Toxicity Criteria (ver.. 4.0). Treatment-related mortality was defined as death due to an adverse effect of a treatment, or by any cause other than lymphoma progression within 1 month of the last R-CHOP cycle. Treatment discontinuation indicated that the pre-planned schedule of R-CHOP was not completed regardless of the reason, other than progressive disease. Pretreatment AGR was calculated using the following equation: AGR = albumin/(total protein–albumin).

2.3. Statistical analysis

A receiver operating curve (ROC) analysis was performed to identify the optimal discriminatory cut-off value of pretreatment AGR for survival. Chi-square or Fisher's exact test was performed for categorical variables, and the Mann–Whitney *U* test for continuous variables, to compare the baseline characteristics between the high and low AGR groups. Overall survival (OS) was defined as the time from the beginning of treatment to death from any cause or the last follow-up. Progression-free survival (PFS) was defined as the time from the beginning of treatment to first progression, death from any cause, or the last follow-up. The Kaplan–Meier method was used to determine OS and PFS, and differences were assessed with the log-rank test. Logistic and Cox regression models were used to adjust for potential confounders of the treatment response and survival in multivariate analyses, respectively. All potential confounders ($p < 0.10$) in univariate analyses were included in the multivariate analysis. A p-value < 0.05 was considered significant in all analyses. All analyses were performed using SPSS software (ver. 18.0; SPSS Inc., Chicago, IL, USA) and MedCalc (ver. 7.2; MedCalc Software, Mariakerke, Belgium).

3. Results

3.1. Clinical characteristics

This study included 232 patients who met the eligibility criteria. Of these, 100 (43.1%) were female, and their median age was 69 years (interquartile range: 58–88 years). In total, 96 (41.4%) patients were aged ≤ 60 years, and 138 (59.5%) had an elevated LDH level. About half of the patients (130/232, 56.0%) were Ann Arbor stage III–IV, 41 (17.7%) had bulky disease, and 33 (14.2%) had BM involvement.

3.2. Cut-off values for the AGR

The ROC curve analysis determined that 1.22 was the AGR cut-off level for survival with an area under the curve (AUC) of 0.693 (95% confidence interval [CI] = 0.629–0.752, $p < 0.001$). The AGR of 1.22 corresponded to the maximum joint sensitivity and specificity on the ROC curve (58.95% and 72.26%, respectively).

3.3. Association between the AGR and the clinical characteristics

Of the 232 patients enrolled in this study, 139 (59.9%) had a high AGR. Significant differences were observed in the baseline characteristics between the low and high AGR groups (Table 1). The low AGR group was older (age > 60 years, 74.2% vs. 48.2%; $p < 0.001$), had poorer PS (ECOG PS 2–3, 43.0% vs. 18.7%; $p < 0.001$), a higher proportion of B symptoms (present, 31.2% vs. 10.8%; $p < 0.001$), a higher serum LDH level (elevated, 74.2% vs. 49.6%; $p < 0.001$), a more advanced Ann Arbor stage (stage III–IV, 66.7% vs. 48.9%; $p = 0.010$), more ENI (> 1 site, 46.2% vs. 27.3%; $p = 0.003$), and higher BM involvement (present, 21.5% vs. 9.4%; $p = 0.012$), compared with the high AGR group. However, no significant differences in bulky disease, gender, or COO were observed between the groups (Table 1).

3.4. Treatment response

Data for the treatment response were obtained for 213 of 232 patients. The remaining 19 patients could not be assessed for the following reasons: early discontinuation of treatment due to treatment toxicity after the first chemotherapy cycle (n = 8), withdrawal from treatment by the patient's refusal (n = 5), early transfer to another hospital (n = 2), and loss to follow-up before the first evaluation of treatment response (n = 4). These patients were considered to have failed to achieve a complete response (CR); the analyses for treatment response were performed on 232 patients. The CR rate was significantly