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Pre-treatment red blood cell distribution width provides prognostic information in multiple myeloma☆

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ABSTRACT

Background: The red blood cell distribution width (RDW), a credible marker for abnormal erythropoiesis, has recently been studied as a prognostic factor in oncology, but its role in multiple myeloma (MM) hasn't been thoroughly investigated.

Methods: We performed a retrospective study in 162 patients with multiple myeloma. Categorical parameters were analyzed using Pearson chi-squared test. The Mann-Whitney and Wilcoxon tests were used for group comparisons. Comparisons of repeated samples data were analyzed with the general linear model repeated-measures procedure. The Kaplan–Meier product-limit method was used to determine OS and PFS, and the differences were assessed by the log-rank test.

Results: High RDW baseline was significantly associated with indexes including haemoglobin, bone marrow plasma cell infiltration, and cytogenetics risk stratification. After chemotherapy, the overall response rate (ORR) decreased as RDW baseline increased. In 24 patients with high RDW baseline, it was revealed RDW value decreased when patients achieved complete remission (CR), but increased when the disease progressed. The normal-RDW baseline group showed both longer overall survival (OS) and progression-free survival (PFS) than the high-RDW baseline group.

Conclusion: Our study suggests pre-treatment RDW level is a prognostic factor in MM and should be regarded as an important parameter for assessment of therapeutic efficiency.

1. Introduction

Red blood cell distribution width (RDW) is routinely measured in the complete blood cell count test, which reflects the degree of heterogeneity of erythrocyte volume, also known as anisocytosis. It is simply calculated by dividing standard deviation of the erythrocytes with the mean corpuscular volume (MCV) of red blood cell (RBCs). It has been regarded as an inexpensive parameter for abnormal erythropoiesis, which is traditionally used for the differential diagnosis of anaemia, and was later found to be closely related to inflammatory (including infection and non-infection) diseases, kidney impairment and malnutrition [1–3]. Meanwhile, this laboratory index has diagnostic and prognostic value in both haematological malignancies [4–8] and solid tumours [9,10].

Multiple myeloma (MM) is the second most common haematological malignancy with an age-adjusted incidence of six per 100,000 per year in the USA and Europe [11]. It is an incurable haematological malignancy characterized by the clonal proliferation of malignant plasma cells within the bone marrow, which results in over-production of monoclonal protein (M-protein) and causes organ and system damage, which results in anaemia, hypercalcemia, renal dysfunction and lytic bone disease. The prognostic factors associated with multiple myeloma, including severe anaemia, hypercalcemia, high serum myeloma protein level and high serum free light chain (sFLC) level [12,13], mainly reflect plasma cell burden or intrinsic characteristics of the myeloma clones. Clinically, evaluations, including bone marrow biopsy and fluorescence in situ hybridization (FISH), are routinely required after treatment starts. Recently, liquid biopsy has been introduced as a new popular concept in oncology based on the discovery of circulating cell-free DNA (cfDNA) and advances in the sensitivity and accuracy of DNA analysis, which indicate the requirement of non-invasive methods in clinic for disease assessment [14,15]. For patients with haematological malignancies, bone marrow biopsy is always painful and inconvenient. Thus, it would very practical to develop new, non-invasive strategies for treatment and evaluation.

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Microenvironment dysfunction is one of the important mechanisms in the pathogenesis of multiple myeloma in recent years [16–18]. As the main original site of erythropoiesis, changes including hypoxia and cytokine dysregulation in the bone marrow (BM) microenvironment due to oncogenesis may impact the quality of erythrocytes. Based on this hypothesis, we performed a retrospective study of clinical multiple myeloma patients to investigate the prognostic value of baseline RDW levels at diagnosis and the relationship between changes in the RDW level and the state of disease after treatment.

2. Patients and methods

2.1. Patients

This analysis included patients with multiple myeloma who were diagnosed and treated at the Drum Tower Hospital (JiangSu, China) between 2008 and 2016. Patients older than 40 years with previously untreated multiple myeloma who did not have severe infections at the first admission and were later administered at least three doses of systemic Bortezomib-based chemotherapy and had complete blood cell test results available before treatment were enrolled. Medical records and laboratory results were retrospectively reviewed. As a result, data from 162 patients and 1440 administrations were collected. Patients were diagnosed by experienced haematologists using the IMWG criteria [19]. The clinical data of the patients, including sex, age, symptoms, myeloma subtype, disease stage based on ISS or D-S, haemoglobin, serum β-2 microglobulin (B2M), serum calcium, serum creatinine, serum albumin, serum lactate dehydrogenase (LDH), presence of lytic bone lesions, bone marrow (BM) plasma cell infiltration, serum protein electrophoresis (SPE), immunofixation, flow cytometry, fluorescence in situ hybridization (FISH) and chromosome results were measured at the time of diagnosis, and some were retested after treatment. Cytogenetic risk groups were defined as follows: unfavorable [t (14;16), del(17p), and t (14;20)]; intermediate risk[t (4;14), hypodiploid and del(13)]; and favorable, which includes all other karyotypic aberrations or a normal karyotype. The symptoms of MM were divided into three categories: localized pain, systematic symptoms and others. Localized pain was defined as pain restricted to a particular area of the body which could be caused by bone lesions or mass compression effects. Systematic symptoms included weight loss, fatigue, nausea, loss of appetite, constipation, palpitation, weakness or loss of feeling in the legs, dizziness, confusion, excessive thirst and frequent infections. Other symptoms were defined as abnormalities in blood tests or body mass that did not cause abnormal feelings of the patients.

This research was approved by the Ethical Committee of Nanjing Drum Tower Hospital of Nanjing University. Informed consent was acquired from each participate before the operation. Each patient had signed written informed consent.

2.2. Measurement of RDW

The baseline RDW level at diagnosis was defined as the value obtained on the nearest day within 10 days before the first-line treatment. RDW was measured using Sysmex (xs-500i). RDW was defined as a parameter of variation (percentage) of red blood cell volume. The reference range for RDW in our centre was 11.0% to 14.0%. We defined the RDW level as “high” when it was over 14.0%.

2.3. Definitions

The primary endpoints of this study were overall survival (OS) and progression-free survival (PFS). OS was defined as the time from initial diagnosis to death or the last follow-up and PFS was defined as time from initial diagnosis to the date of progression, relapse or death. Patients who were lost to follow-up were censored at the date of last contact. Based on the uniform response criteria of IMWG, the primary response categories in this study were complete response (CR), very good partial response (VGPR), PR, stable disease (SD), progressive disease (PD) and relapse [20].

2.4. Statistics

Patients were divided into two groups: high-RDW group and normal-RDW group, according to the RDW value. Patients' characteristics were compared between the two groups. Categorical parameters were analyzed using Pearson chi-squared test. The Mann-Whitney and Wilcoxon tests were used for group comparisons. Comparisons of repeated samples data were analyzed with the general linear model repeated-measures procedure. The Kaplan–Meier product-limit method was used to determine OS and PFS, and the differences were assessed by the log-rank test. All data were statistically analyzed using a commercially available statistical software package (SPSS 19.0; IBM Corp.). Differences were considered statistically significant when P values were < 0.05.

3. Results

3.1. Patients characteristics

A total of 162 patients were eligible for this analysis. The median age was 61 (40–87) years, and 87 (53.7%) were male. The median baseline RDW level was 14.6% (range from 11.4% to 31.1%, mean level 15.3%). Among these, 97 (60.5%) patients presented with a higher pre-treatment RDW level than the upper limit of the normal range ($> 14.0\%$). The mean RDW values of the normal-RDW group and high-RDW group were 13.1% (range, 11.4–14%; median, 13.2%) and 16.7% (range, 14.4–31.1%; median, 15.9%), respectively. Characteristics of the patients categorized according to the pre-treatment RDW level are presented in Table 1.

The baseline RDW level was correlated to haemoglobin, albumin level, platelet count, symptoms (subgrouped into localized pain, systematic symptoms including weakness, dizziness, nausea, chest tightness, elevated globulin and the presence of a painless mass), bone marrow plasma cell infiltration, and International Staging System (ISS) stage [21]. On the other hand, the distribution of sex, age, and comorbidities, including diabetes mellitus, hypertension, cardiovascular diseases, malignancies, chronic liver disease, and chronic pulmonary diseases, creatinine level, β2-microglobulin, lactate dehydrogenase level, heavy or light chain type and bone disease were not different between the two groups. Age, CRP level, bone marrow plasma cell infiltration at diagnosis, ISS stage and Durie-Salmon (D-S) stage have all been reported as prognostic factors for MM patients in clinic. In our study, we analyzed the distribution of RDW baseline in the different groups mentioned above. It was revealed that RDW values between different ages and CRP levels subgroup were not significantly different, but between the bone marrow plasma cell infiltration $\leq 30\%$ and bone marrow plasma cell infiltration $> 30\%$ groups and subgroups within the ISS and D-S stages, the differences were statistically significant (Fig. 1). It has been reported that immunophenotypes including CD117, CD19, and CD45 are related to prognosis, but there was no significant difference of RDW baseline between the negative and positive groups (Fig. 2).

3.2. Response after introduction

Eleven patients, who didn't receive > 2 courses of Bortezomib-based chemotherapy, were excluded. Among 151 patients who responded to the chemotheraphy (including partial remission, PR, very good partial remission, VGPR and complete remission, CR) during the induction, the overall remission rate (ORR) decreased as the RDW baseline increased. Though there is no difference between groups ($P = 0.051$) (Table 2).