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Case Control Study

Reduction rate of M protein as a useful prognostic factor in standard-risk group of newly diagnosed multiple myeloma

The reduction rate of M protein

Min Liu, Jun-Yu Zhang

BACKGROUND

Multiple myeloma (MM) is a common hematologic malignancy that originate from a malignant clone of plasma cells. Solitary plasmacytoma, history of diabetes, and platelet count were considered as prognostic factors of MM. But some patients are still associated with much worse outcomes without any prognosis. This study aimed to observe the reduction rate of monoclonal (M) protein after the first and fourth chemotherapy cycles, which is considered as a new prognostic factor for progression-free survival (PFS) in standard- risk group of newly diagnosed MM patients.

AIM

Investigate the reduction rate of M protein after first and fourth cycle chemotherapy as a useful prognostic factor.

METHODS

A total of 316 patients diagnosed with MM for the first time between 2010 and 2019 at the Municipal Central Hospital were included. All patients were diagnosed according to the National Comprehensive Cancer Network(NCCN 2020.V1) diagnostic criteria. The

risk group divided by mSMART guideline. After diagnosis, 164 patients who were evaluated and underwent treatment with four to eight courses of continuous induction chemotherapy. The patients with no response after induction treatment were administered additional therapy followed by NCCN 2020.V1. The baseline data from the patients were collected: gender, age at diagnosis, Durie–Salmon (DS) stage, glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), catabolite activator protein (CRP), albumin/globulin, lactate dehydrogenase (LDH), t(6;14), t(11;14), maintenance regimen, total cholesterol (TC), triglyceride (TG), phosphorous (P). ALL baseline datas and the reduction rate of M protein after each chemotherapy cycle from first to fouth were analyzed in univariate analysis. The factors influencing the OS and PFS were analyzed in multivariate analysis. We found C1 reduction rate and C4 reduction rate were considered as predictors of PFS. Then patients were compared PFS of the groups in reduction rate of M protein after first chemotherapy of ≥25% and <25%. Then compared PFS of the groups in reduction rate of M protein after first chemotherapy of ≥50% and <50%. We also compared PFS of the groups in C4 reduction rate of ≥25% *vs* <25%, ≥50% *vs* <50% and ≥75% *vs* <75%.

RESULTS

Multivariate analysis revealed the age (HR: 1.059, 95%CI: 1.033-1.085, P≤0.001), ISS stage (HR: 2.136, 95%CI: 1.500-3.041, P≤0.001), autotransplantion (HR: 0.201, 95%CI: 0.069-0.583, P = 0.019), TC (HR: 0.689, 95%CI: 0.533-0.891, P = 0.019), C1 reduction rate (HR: 0474, 95%CI: 0.293-0.767, P = 0.019), and C4 reduction rate (HR: 0.254, 95%CI: 0.139-0.463, P = 0.019) were considered as predictors of PFS. The K–M curve and the log-rank tests revealed that the high reduction rate of M protein after first cycle (≥50%) and fourth cycle(≥75%) chemotherapy was longer than the lower group.

CONCLUSION

Higher reduction rate of M protein after first and fourth chemotherapy cycles act as advantageous prognostic factors for PFS in standard- risk group of MM patients during initial diagnosis.

Key Words: Multiple myeloma; Monoclonal protein; Progression-freesurviva; Chemotherapy

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Core Tip: Multiple myeloma (MM) is a common hematologic malignancy that originate from a malignant clone of plasma cells. Solitary plasmacytoma, history of diabetes, and platelet count were considered as prognostic factors of MM. But some patients are still associated with much worse outcomes without any prognosis. This study aimed to observe the reduction rate of monoclonal (M) protein after the first and fourth chemotherapy cycles, which is considered as a new prognostic factor for progression-free survival (PFS) in standard- risk group of newly diagnosed MM patients.

INTRODUCTION

Multiple myeloma (MM) is the second common hematologic malignancy that originate from B cell, and accounted for approximately 1.8% of all malignancies and led to death of 30 000 patients in 2018[1]. This subsequently caused kidney injury, anemia, lytic bone disease, hypercalcemia, abnormal functioning of blood coagulation and damage of other organs [2]. Bone pain is the most common symptom that significantly impaired the quality of life in approximately 60% of patients[3]. For over the past decade, many studies have revealed nonoverlapping and overlapping genetic abnormalities in the myeloma cells and also demonstrated the impact of it on patient outcomes[4-5]. Del17p, t(4;14), t(14;16), t(14;20) were considered as predictors of significantly shortened survival in patients with newly diagnosed MM[6-9]. In addition, according to the geriatric assessment[10], due to the

absence of high-risk cytogenetic abnormalities[11], both the International Staging System (ISS) and the Revised-ISS (R-ISS) act as prognostic factors for the overall survival (OS) and progression-free survival (PFS) in patients. And ISS 1 and R-ISS 1 patients enjoy a significantly longer PFS and OS[12-13], while conventional factors such as age below 80 years, beta-2-microglobulin (β2M) levels, normal hemoglobin (Hb) and normal lactate dehydrogenase (LDH) levels were identified as predictors for PFS and OS[14-15]. However, the median survival of patients with MM showed great improvement after undergoing chemotherapy, which consists of proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies[16], while few patients without these predictors still demonstrated poorer outcome. Our research revealed that the reduction rate of M protein after first and fourth chemotherapy cycles could act as new advantageous prognostic factors for PFS in in standard- risk group of MM patients during initial diagnosis.

MATERIALS AND METHODS

A total of 316 patients diagnosed with MM for the first time between 2010 and 2019 at the Municipal Central Hospital were included. All patients were diagnosed according to the National Comprehensive Cancer Network(NCCN 2020.V1) diagnostic criteria. The risk group divided by mSMART guideline. After diagnosis, 164 patients who were evaluated and underwent treatment with four to eight courses of continuous induction chemotherapy. The patients with no response after induction treatment were administered additional therapy followed by NCCN 2020.V1. The baseline data from the patients were collected: gender, age at diagnosis, Durie–Salmon (DS) stage, glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), catabolite activator protein (CRP), albumin/globulin, lactate dehydrogenase (LDH), t(6;14), t(11;14), maintenance regimen, total cholesterol (TC), triglyceride (TG), phosphorous (P). ALL baseline datas and the reduction rate of M protein after each chemotherapy cycle from first to fouth were analyzed in univariate analysis. The factors influencing the OS and PFS were analyzed in multivariate analysis. We found C1 reduction rate and C4 reduction rate were considered as predictors of PFS. Then patients were compared PFS

of the groups in reduction rate of M protein after first chemotherapy of ≥25% and <25%. Then compared PFS of the groups in reduction rate of M protein after first chemotherapy of ≥50% and <50%. We also compared PFS of the groups in C4 reduction rate of ≥25% *vs* <25%, ≥50% *vs* <50% and ≥75% *vs* <75%.

RESULTS

Patient characteristics

We retrospectively analyzed data from a total of 164 patients in this study, and all patients underwent treatment with four to eight courses of continuous induction chemotherapy. The median observation time was 48.4 mo (range of 9～114 mo). The distribution of baseline characteristics for 164 MM patients diagnosed for the first time based on the reduction rate of M protein after first and fourth chemotherapy cycles are presented in Table 1. The results showed no significant differences in gender, Durie–Salmon (DS) stage, glutamic-pyruvic transaminase (GPT), glutamic-oxaloacetic transaminase (GOT), catabolite activator protein (CRP), lactate dehydrogenase (LDH), t(6;14), t(11;14), maintenance regimen, total cholesterol (TC), triglyceride (TG), phosphorous (P) concentrations between the groups in the reduction rate of M protein after first and fourth chemotherapy cycle (**Table 1**).

Prognostic impact of the reduction rate of M protein after first and fourth cycle chemotherapy for standard- risk group of newly diagnosed MM

Tables 2 showed the results of the univariate analysis of the factors influencing the OS and PFS, respectively. Multivariate analysis revealed the age (HR: 1.059, 95%CI: 1.033-1.085, P≤0.001), ISS stage (HR: 2.136, 95%CI: 1.500-3.041, P≤0.001), autotransplantion (HR: 0.201, 95%CI: 0.069-0.583, *P* = 0.019), TC (HR: 0.689, 95%CI: 0.533-0.891, *P* = 0.019), C1 reduction rate (HR: 0474, 95%CI: 0.293-0.767, *P* = 0.019), and C4 reduction rate (HR: 0.254, 95%CI: 0.139-0.463, *P* = 0.019) were considered as predictors of PFS (**Table 3**).

The K–M curve and the log-rank tests revealed there was no difference between the two groups that the reduction rate of M protein after first chemotherapy of ≥25% and <25% (*P* = 0.319), but have significant differences between the groups that the reduction rate of

M protein after first chemotherapy of ≥50% and <50% (P≤0.001), (Figure 1). The K–M curve and the log-rank tests also showed that PFS was no difference between the groups of the reduction rate of M protein after fourth chemotherapy of ≥25% *vs* <25% ($P = 0.248$), the same is true in the groups of ≥50% *vs* <50% ($P = 0.228$). It revealed significant differences between the two groups that the reduction rate of M protein after fourth chemotherapy of ≥75% and <75% (P≤0.001) (Figure 2).

Age (HR: 1.054, 95% confidence Interval: 1.027-1.081, $P = 0.024$), ISS stage (HR: 1.879, 95% confidence Interval: 1.315-2.686, $P = 0.001$), platelet count (HR: 2.929, 95% confidence Interval: 1.269-6.756, $P = 0.012$), autotransplantion (HR: 0.211, 95% confidence Interval: 0.069-0.647, $P = 0.006$), and TC (HR: 0.735, 95% confidence Interval: 0.573-0.943, $P = 0.016$) act as dependent predictors of OS (**Table 4**).

DISCUSSION

MM is a heterogeneous disease with adverse clinical course, and is characterized by uncontrolled proliferation and accumulation of plasma cells in the bone marrow, which is usually connected with the production of monoclonal protein and is expressed by differences in the effectiveness of therapeutic strategies and the ability to develop chemoresistance. The risk stratification factors assist in creating a fit and personalized therapy, thereby improving the treatment outcomes. Prognostic markers such as cytogenetics, molecular biology, and ISS stage showed association with OS and PFS in MM patients[17]. But there are still many patients with much worse outcomes and without any prognostic markers. This study aimed to find more prognostic markers that might help doctors to adjust the therapeutic strategiesin time.

M-protein refers to monoclonal immunoglobulins or fragments created by abnormal monoclonal B cell or plasma cell to define ISS stage in the prognostic outcome of MM[12-13]. Its deposition could cause destruction of organs such as renal and skin[18]. The M-protein level as clonal burden is considered to be helpful in predicting the risk of progression of monoclonal gammopathy of undetermined significance (MGUS) to symptomatic diseases[19]. Furthermore, monoclonal gammopathy could affect BM

microenvironment, resulting in increased risk of infections, osteoporosis, venous and arterial thrombosis, and bone fractures[19]. In addition, the M-protein production that has autoantibody activity or its deposition in tissues is considered responsible for severe organ damage[19]. González-Calle V et al have found Bence Jones proteinuria as a kind of M-protein, and acts as a tumor burden marker, showing significant association with the risk of progression to symptomatic progression[20]. Jo Caers' s study demonstrated M-protein as a significant risk factor in most of the patients with Smoldering multiple myeloma (SMM) turning into MM[21]. Another study from Spain revealed that M-protein with an increase of ≥10% in the first 12 mo of diagnosis showed progression to symptomatic MM by 71% at 3 years with a median period of 1.1 year[22]. Susanna Gassiot *et al* showed the number of patients presenting both a prior MGUS/SMM and PR (PR was defined as ≥90% reduction of urinary M protein in 24h or <200mg per 24h and reduction of ≥50% of serum M protein) after first cycle of therapy, and the PFS and OS showed significant differences from the remaining patients[23]. The study also revealed that a fast response to the first treatment cycle in MM patients would also support the same concept[23]. Catherine Atkin et al have thought that the M-protein production is reduced by treatment with chemotherapy, improving the MGUS' outcomes[24].

In this retrospective analysis, the outcome of intermediate and intermediate and standard-risk chromosomal abormalities group of newly diagnosed MM patients with those who obtained a reduction rate of M protein after first chemotherapy cycle in ≥50% were compared with those who obtained in <50%, and the reduction rate of M protein after fourth chemotherapy cycle in ≥75% were compared with those in <75% groups.

Our study showed that the median PFS in patients with lower reduction rate in two stages were 20 and 18 mo, while with higher reduction rate were 33 and 30 mo. A PFS rate of 36 mo showed significant differences between the lower and higher groups in the two stages. In multivariate analysis, a higher reduction rate in the two stages was shown to be as an advantageous factor for PFS, and the reduction rate of M protein after fourth chemotherapy cycle in ≥75% protection was stronger. Although the reduction rate of M protein after first and fourth chemotherapy cycles do not act as a dependent prognostic

factor for OS in multivariate analysis, the trend of higher reduction rate after fourth chemotherapy cycle (≥75%) achieved a longer OS. It has been more than 30 years of connection of chemotherapy to autologous stem cell transplantation (ASCT), which remained to be a standard care for few patients with newly diagnosed MM[25-27]. Our study also supported this, and ASCT after chemotherapy was regarded as protective factor for both PFS and OS. This might be one of the reasons for the association of high reduction rate with longer PFS. After obtaining a high reduction rate, more patients had chance to connect to ASCT. Furthermore, our study found TC as a protective factor for both PFS and OS. MA Congcong's research demonstrated that the cholesterol level was associated with MM[28]. Jafri H *et al* also revealed an inverse correlation with cholesterol level to hematologic malignancy[29]. The mechanism still remained unclear. Previous study revealed that the low platelet count is associated with unfavorable significance of OS[30]. Compared to previous studies, high ISS stage and age were considered as disadvantageous factors for PFS and OS[31-33].

CONCLUSION

Our study found new dependent prognostic factors for patients with initial diagnosed MM, and the high reduction rate of M protein after first chemotherapy cycle (≥50%), and fourth chemotherapy cycle (≥75%) achieved longer PFS. The high reduction rate of M protein after fourth chemotherapy cycle could affect the OS. To our knowledge, this is the first study to analyze the effects of reduction rate of M protein after chemotherapy in MM patients. The new prognostic factors could help doctors to conduct the treatment in time.

ARTICLE HIGHLIGHTS

Research background

Multiple myeloma (MM) is a common hematologic malignancy that originate from a malignant clone of plasma cells. Solitary plasmacytoma, history of diabetes, and platelet

count were considered as prognostic factors of MM. But some patients are still associated with much worse outcomes without any prognosis.

Research motivation

This study aimed to observe the reduction rate of monoclonal (M) protein after the first and fourth chemotherapy cycles, which is considered as a new prognostic factor for progression-free survival (PFS) in standard- risk group of newly diagnosed MM patients.

Research objectives

This study aimed to observe the reduction rate of monoclonal (M) protein after the first and fourth chemotherapy cycles, which is considered as a new prognostic factor for progression-free survival (PFS) in standard- risk group of newly diagnosed MM patients.

Research methods

We retrospectively analyzed 164 patients diagnosed with standard- risk group of MM for the first time, compare the PFS and overallsurvival （OS） of the group in the reduction rate of M protein after first chemotherapy of ≥50% and the group in the reduction rate of M protein after first chemotherapy of <50%. Also compare the PFS and OS of the group in the reduction rate of M protein after fourth chemotherapy cycle ≥75% and the group in the reduction rate of M protein after fourth chemotherapy of <75%.

Research results

Multivariate analysis revealed the age (HR: 1.059, 95%CI: 1.033-1.085, P≤0.001), ISS stage (HR: 2.136, 95%CI: 1.500-3.041, P≤0.001), autotransplantion (HR: 0.201, 95%CI: 0.069-0.583, P = 0.019), TC (HR: 0.689, 95%CI: 0.533-0.891, P = 0.019), C1 reduction rate (HR: 0474, 95%CI: 0.293-0.767, P = 0.019), and C4 reduction rate (HR: 0.254, 95%CI: 0.139-0.463, P = 0.019) were considered as predictors of PFS. The K–M curve and the log-rank tests revealed that the high reduction rate of M protein after first cycle (≥50%) and fourth cycle(≥75%) chemotherapy was longer than the lower group.

Research conclusions

Our study found new dependent prognostic factors for patients with initial diagnosed MM, and the high reduction rate of M protein after first chemotherapy cycle (≥50%), and fourth chemotherapy cycle (≥75%) achieved longer PFS. The high reduction rate of M protein after fourth chemotherapy cycle could affect the OS.

Research perspectives

To our knowledge, this is the first study to analyze the effects of reduction rate of M protein after chemotherapy in MM patients. The new prognostic factors could help doctors to conduct the treatment in time.

Figure Legends

Figure 1. The K–M curve and the log-rank tests of PFS for patients with different reduction rates of M protein after the first cycle of chemotherapy (P<0.001). a: The PFS for the two groups in which the reduction rate of M protein after first chemotherapy was ≥25% and <25%. b: The PFS for the two groups in which the reduction rate of M protein after first chemotherapy was ≥50% and <50%.

Figure 2. The K–M curve and the log-rank tests of PFS for patients with different reduction rates of M protein after the fourth cycle of chemotherapy (P<0.001). a: The PFS for the two groups with a reduction rate of M protein after the first chemotherapy cycle of ≥25% and <25%. b: The PFS for the two groups in which the reduction rate of M protein after first chemotherapy was ≥50% and <50%. c: The PFS for the two groups in which the reduction rate of M protein after first chemotherapy was ≥75% and <75%.

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