The reduction rate of M protein after first and fourth cycle chemotherapy predicts the outcome in patients initially diagnosed with multiple myeloma

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Abstract

Background: Multiple myeloma (MM) is a hematologic malignancy that originate from a malignant clone of plasma cells. This study aimed to discover the reduction rate of monoclonal (M) protein after first and fourth cycle chemotherapy, which acts as a new prognostic factor for progression-free survival (PFS) in MM patients.

Methods: We retrospectively analyzed 164 patients with MM. The overall survival (OS) and PFS from the time of first diagnosis were measured. Cox proportional hazards model was used to evaluate if the reduction rate of M protein after first to fourth cycle chemotherapy effect PFS and OS.

Results: Multivariate analysis was performed with factors including del(17p), t(14;16), t(14;20), ISS stage, age, AST and others parameters. The reduction rate of M protein after first cycle chemotherapy (C1 reduction rate) (P<0.001) and the reduction rate of M protein after fourth cycle chemotherapy (C4 reduction rate) (P<0.001) acts as dependent predictors of PFS. The 36 months PFS rate in patients with a reduction rate of M protein after the first cycle chemotherapy was compared. The reduction rate of ≥25 vs <25% showed no difference, while the reduction rate of ≥50 vs <50% showed significant difference in PFS. Meanwhile, the reduction rate of M protein after the fourth cycle chemotherapy ≥25 vs <25%, ≥50 vs <50% showed no meaning, but the groups of ≥75 vs <75% showed significant differences in PFS. The patients with higher reduction rate in these two stages had longer PFS.

Conclusions: Higher reduction rate of M protein after first and fourth cycle of chemotherapy act as advantageous prognostic factors for PFS in MM patients in the initial diagnosis.

Background

Multiple myeloma (MM) is the second common hematologic malignancy that originates from B cell, and account for approximately 1.8% of all malignancies and led to death of 30 000 patients in 2018[1]. This subsequently causes kidney injury, anemia, lytic bone disease, hypercalcemia, abnormal functioning of blood coagulation and others organs damage[2]. Bone pain is the most common symptom that significantly impair the patients’ 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 cell and also demonstrated the impact of it on patient outcome[4–5]. Del17p, t(4;14), t(14;16), t(14;20) have been shown to be as predictors for the significantly shortened survival in patients with newly diagnosed MM[6–9]. In addition, according to 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 overall survival (OS) and progression-free survival (PFS). Patients with ISS 1 and R-ISS 1 enjoy a significantly longer PFS and OS[12–13]. Otherwise, conventional factors such as age below 80 years, beta-2-microglobulin (β2M) levels, normal hemoglobin (Hb) and normal lactate dehydrogenase (LDH) levels were also 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 have poorer outcome. Our research revealed that the reduction rate of M protein after first and fourth cycle of chemotherapy could act as new advantageous prognostic factors for PFS in the initial diagnosis of MM.

Methods

Ethics statement

Research was conducted in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Medical Research and Ethics Committee of the Lishui Municipal Central Hospital. All patients have signed the relevant informed consent form.

Patients

A total of 181 patients diagnosed with MM for the first time between 2010 and 2019 at the Municipal Central Hospital were included. After diagnosis, 164 patients were evaluated and underwent treatment with four to eight courses of continuous induction chemotherapy every 4 weeks with VCD regimen (bortezomib, cyclophosphamide, dexamethasone), VRD regimen (bortezomib, lenalidomide, dexamethasone), PAD regimen (bortezomib, liposomal doxorubicin, dexamethasone), TCD regimen (thalidomide, cyclophosphamide, dexamethasone), VAD regimen (vincristine, Adriamycin, dexamethasone). A part of patients underwent evaluation by tandem autologous stem cell transplant.
All patients received maintenance therapy by either immunomodulatory drugs like thalidomide, lenolidomide or bortezomib followed by induction therapy. Lactating or pregnant women were excluded from this study.

**Study objectives**

The M protein was measured after each course of chemotherapy. The reduction rate of M protein after the first cycle chemotherapy was calculated by the original M protein value minus the M protein value measured before the second chemotherapy / the original M protein value. The reduction rate of M protein after second cycle chemotherapy was calculated by the original M protein value minus M protein value measured before third chemotherapy / the original M protein value. The reduction rate of M protein after third cycle chemotherapy was calculated by the original M protein value minus M protein value measured before fourth chemotherapy / the original M protein value. The reduction rate of M protein after fourth cycle chemotherapy was calculated by the original M protein value minus M protein value measured before fifth chemotherapy / the original M protein value. Complete remission (CR) was defined as patients with (1) ≤5% plasma cells in the bone marrow (BM); (2) disappearance of any soft tissue plasmacytomas; and (3) negative immunofixation on serum and urine. Very good partial response (VGPR) was defined as patients with 90% or more than 90% reduction in the serum M protein level plus urine M protein level <100mg per 24h or M protein (Serum and urine) detected by immunofixation. Partial response (PR) was defined as patients with ≥90% reduction of urinary M protein within 24hrs to <200mg per 24h and reduction of ≥50% of serum M protein, and if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas. The primary endpoints were OS and PFS. PFS was measured from the time of first diagnosis till disease progression. Progressive disease was defined as an increase of 25% of one of the following criteria from the lowest confirmed response value: (1) serum M protein increase of ≥1 g/dl, if the lowest M component was ≥5 g/dl; (2) serum M protein (absolute increase must be ≥0.5 g/dl); or (3) urine M protein (absolute increase must be ≥200 mg/24 h). OS was defined as the time from first diagnosis until death or last follow-up visit.

**Statistical analysis**

The data were analyzed using SPSS21. The reduction rate of M protein after first to fourth cycle
chemotherapy and clinical parameters was assessed by chi square test. PFS and OS were estimated by Kaplan-Meier method and log-rank test. Cox proportional hazards model was constructed for analyzing PFS and OS. A stepwise selection method was used to determine the potential confounding covariates. The hazard ratio (HR) was estimated to assess the association of risk factors with PFS and OS. A P value of less than 0.05 was considered to be statistically significant.

Results

Patient characteristics

We retrospectively analyzed data from a total of 181 patients in this study, 164 patients of these underwent treatment with four to eight courses of continuous induction chemotherapy. The median observation time was 48.4 months (range of 9–114 months). 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 cycle chemotherapy 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), albumin/globulin, lactate dehydrogenase (LDH), t(6;14), t(11;14), t(14;16), maintenance regimen, total cholesterol (TC), triglyceride (TG), phosphorous (P) concentrate between the groups of reduction rate of M protein after first chemotherapy of ≥50% versus vs <50% and the reduction rate of M protein after fourth chemotherapy ≥75% vs <75% (Table 1).

Higher reduction rate of M protein after first cycle and fourth cycle chemotherapy act as adverse prognostic factors for progression-free survival of multiple myeloma during initial diagnosis

The parameters such as age (PFS: P=0.000; OS: P=0.002), ISS stage (PFS: P=0.001; OS: P=0.000), DS stage (PFS: P=0.028; OS: P=0.045), GOT (PFS: P=0.000; OS: P=0.000), LDH (PFS: P=0.000; OS: P=0.000), UA (PFS: P=0.000; OS: P=0.000), del(17p) (PFS: P=0.000), t(14;16) (PFS: P=0.000; OS: P=0.028), t(14;20) (PFS: P=0.002; OS: P=0.028), t(4;14) (PFS: P=0.000; OS: P=0.000), platelet count (PFS: P=0.000; OS: P=0.000), autotransplantation (PFS: P=0.020; OS: P=0.022), TC (PFS: P=0.013; OS: P=0.007), C1 reduction rate (PFS: P=0.000; OS: P=0.000), C2 reduction rate (PFS: P=0.000; OS:
P=0.000), C3 reduction rate (PFS: P=0.000; OS: P=0.000), and C4 reduction rate (PFS: P=0.000; OS: P=0.000) were significantly associated with PFS and OS. Maintenance regimen (P=0.038), and GPT (P=0.019) were related to PFS (Table 2). When entered into a Cox regression model for multivariate analysis, age (HR: 1.059, 95% confidence Interval: 1.033-1.085, P=0.000), ISS stage (HR: 2.136, 95% confidence Interval: 1.500-3.041, P=0.000), del(17p) (HR: 20.598, 95% confidence Interval: 3.570-118.848, P=0.001), t(14;16) (HR: 3.914, 95% confidence Interval: 1.180-12.978, P=0.019), t(14;20) (HE: 13.988, 95% confidence Interval: 2.438-80.385, P=0.019), t(4;14) (HR: 1.414, 95% confidence Interval: 0.562-3.558, P=0.019), autotransplantion (HR: 0.201, 95% confidence Interval: 0.069-0.583, P=0.019), TC (HR: 0.689, 95% confidence Interval: 0.533-0.891, P=0.019), C1 reduction rate (HR: 0.474, 95% confidence Interval: 0.293-0.767, P=0.019), and C4 reduction rate (HR: 0.254, 95% confidence Interval: 0.139-0.463, P=0.019) were considered as predictors of PFS (Table 3). 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), del(17p) (HR: 6.527, 95% confidence Interval: 1.095-38.893, P=0.039), t(14;16) (HR: 4.874, 95% confidence Interval: 1.344-17.684, P=0.016), t(14;20) (HR: 30.719, 95% confidence Interval: 4.811-196.154, P=0.000), t(4;14) (HR: 4.478, 95% confidence Interval: 1.814-11.061, 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 for OS (Table 4).

The reduction rate of M protein after first cycle chemotherapy affects PFS

PFS was analyzed by using the reduction rate of M protein after first cycle chemotherapy. The patients were divided into two groups, patients with reduction rate of M protein of ≥25% and patients with <25%. The results revealed that the 36 months PFS rate showed no significant difference between the two groups (P=0.319). Then the reduction rate of M protein ≥50 vs <50% was compared. The 36 months PFS rate of the reduction rate of M protein ≥50% after first cycle chemotherapy was significantly higher than the reduction rate <50%, in which one was 44.3% and another was 8.1% (P<0.001). The K-M curve and the log-rank tests revealed significant differences between the two groups (P<0.001), (Figure 1).
**The reduction rate of M protein after fourth cycle chemotherapy affects PFS**

Comparison of PFS on the reduction rate of M protein after fourth cycle chemotherapy ≥25% vs <25%, ≥50% vs <50% and ≥75% vs <75%, and the results revealed that 36 months PFS rate showed no differences between ≥25% vs <25% groups (P=0.248) and ≥50% vs <50% groups (P=0.228). But significant differences were observed between ≥75% vs <75% group. The PFS rate of reduction rate at 36 months ≥75% was 36.9% and was 5.0% in reduction rate <75% (P<0.001). The K–M curve and the log-rank tests revealed that the reduction rate of M protein after fourth cycle chemotherapy in ≥75% PFS was longer than that in <75% (P<0.001), (Figure 2).

**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 a monoclonal protein and is expressed by differences in the effectiveness of therapeutic strategies and ability to develop chemoresistance. The risk stratification factors would help to create a fit and personalized therapy, which thereby improves 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 who have much worse outcome without such prognostic markers. This study aimed to find more prognostic markers that might help doctors to adjust the therapeutic strategies in time.

M-protein refers to monoclonal immunoglobulin or fragment 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 organ destruction, 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 an increased risk of infections, osteoporosis, venous and arterial thrombosis, and bone fractures[19]. In addition, through M-protein production that has autoantibody activity or deposits in tissues also is responsible for severe organ damage[19]. González-Calle V et al have found Bence Jones proteinuria as a kind of M-protein, which acts as a tumor burden marker, that
is significantly associated 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 reported series of patients with Smoldering multiple myeloma (SMM) turning into MM[21]. Another study from Spain assessed M-protein with an increase ≥ 10% in the first 12 months from diagnosis, progression into symptomatic MM rate at 3 years was 71% and median time was 1.1 years[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 24 h or to < 200 mg per 24 h 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 would also support the same concept[23]. Catherine Atkin et al have thought of reducing the M-protein production by treatment with chemotherapy, which in turn can improve the MGUS’ outcomes[24].

In our retrospective analysis, the outcomes of patients were compared with those who obtained a reduction rate of M protein after first cycle chemotherapy ≥ 50% with those who obtained at < 50%, and the reduction rate of M protein after fourth cycle chemotherapy ≥ 75% with those with < 75%. Our study showed that the median PFS in patients with lower reduction rate in two stages were 20 and 18 months, while a higher reduction rate were 33 and 30 months. A PFS rate of 36 months showed significant different between the lower and higher groups in two stages. In multivariate analysis, a higher reduction rate in the two stages was observed to be as an advantageous factor for PFS, and the reduction rate of M protein after fourth cycle chemotherapy in ≥ 75% protection was stronger. Although the reduction rate of M protein after first and fourth cycle chemotherapy do not act as a dependent prognostic factor for OS in multivariate analysis, the trend of higher reduction rate after fourth cycle chemotherapy (≥ 75%) would achieve longer OS. Del(17p), t(14;16), t (14;20) were associated with bad outcomes in multivariate analysis as reported previously, and could affect both PFS and OS[8–9, 25]. The t (6;14) and t (11;14) do not act as outcome factors for PFS and OS in our analysis, and this might be due to that fewer patients had these two cytogenetic abnormalities in our study[26–29]. Maintenance therapy was considered to be a good prognostic factor for PFS in our study[30–32]. It has been more than 30 years of connection of chemotherapy to autologous stem cell
transplantation (ASCT), which remains a standard care for few patients with newly diagnosed MM[33–35]. 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 high reduction rate showed association 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 for both PFS and OS. MA Congcong’s research demonstrated that the cholesterol level was associated with MM[36]. Jafri H et al also revealed inverse correlation of cholesterol level to hematologic malignancy[37]. The mechanism was still unclear. Previous study revealed that the low platelet count is associated with unfavorable significance OS [38]. Compared to previous studies, high ISS stage and age were considered as disadvantageous factors for PFS and OS[39-41].

However, our study still has some limitations, which are as follows: (1) this was a single-center cohort study; (2) the sample size was relatively small. The classification of IgA and IgD was observed in 2 cases and 1 case in our analysis, so the influence of classification and other cytogenetic abnormalities could not be analyzed; (3) chemotherapy regimen consisted of VRD, RD, TD, PAD and so on, and different regimens would affect remission rate, which might lower the quality of the data. So, this requires validation in a larger cohort in the future; and (4) many suitable patients did not undergo ASCT due to several reasons, and this might in turn affect the results.

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

Abbreviations
MM multiple myeloma, Cr creatinine, GPT glutamic-pyruvic transaminase, GOT glutamic-oxaloacetic transaminase, CRP catabolite activator protein, UA uric acid, PLATELET platelet, LDH lactate
dehydrogenase, PCD bortezomib, cyclophosphamide, dexamethasone, PAD bortezomib, adriamycin, dexamethasone, VRD bortezomib, lenalidomide, dexamethasone, VAD vincristine, adriamycin, dexamethasone, TCD thalidomide cyclophosphamide, dexamethasone, PD bortezomib, dexamethasone, TC total cholesterol, TG triglyceride, P phosphorus, PFS progression-free survival, OS overall survival, C4 the fourth cycle chemotherapy, C1 the first cycle chemotherapy.

Declarations

Ethics approval and consent to participate:

Ethics approval: Research involving human participants had been performed in accordance with the Declaration of Helsinki and had been approved by the Medical Research and Ethics Committee of the Lishui Municipal Central Hospital. The statement was as follows:

[See supplementary files for document.]

Consent to participate: ALL participants informed consent to participate in the study had been obtained from participants (or their parent or legal guardian in the case of children under 16).

Consent for publication: Not applicable

Availability of data and materials: Not applicable

Competing interests: The authors declare that they have no competing interests

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Authors' contributions:

JYZ analyzed the clinical data and was a major contributor in writing the manuscript.

LJL was the idea provider and corresponding author. NWX, YC and CJZ were collected clinical data. WEL, YJJ and MLZ analyzed and interpreted the patient data regarding the hematological disease. All authors have read and approved the manuscript.

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Tables
Table 1 Baseline characteristics based on MM patients with a reduction rate of M protein after first and fourth cycles of chemotherapy [the first cycle (C1) reduction rate ≥50 versus <50, the fourth cycle (C4) reduction rate ≥75 versus <75]

| Characteristics | C1 reduction rate | P  | C4 reduction rate | P  |
|-----------------|------------------|----|------------------|----|
|                 | <50 | ≥50 |     | <75 | ≥75 |
| Age (year)      |     |     |     |     |     |
| <65             | 25  | 56  | 0.000 | 21  | 60  | 0.003 |
| ≥65             | 49  | 34  | 0.912 | 40  | 43  | 0.903 |
| Gender          |     |     |     |     |     |
| Male            | 36  | 43  | 0.935 | 37  | 42  | 0.665 |
| Female          | 38  | 47  |     | 39  | 46  |     |
| Classification  |     |     |     |     |     |
| IgG             | 4   | 12  |     | 1   | 15  |     |
| IgGκ            | 19  | 18  |     | 19  | 18  |     |
| IgGλ            | 20  | 21  |     | 18  | 23  |     |
| IgA             | 2   | 0   |     | 1   | 1   |     |
| IgA, κ          | 3   | 3   |     | 2   | 4   |     |
| IgA, λ          | 4   | 13  |     | 3   | 14  |     |
|                  | κ  | 10  | 3   | 7   | 6   |
|------------------|----|-----|-----|-----|-----|
|                  | λ  | 12  | 19  | 10  | 21  |
|                  | IgD| 0   | 1   | 0   | 1   |
|                  | ISS|     | 0.000 | 0.000 |
| I                | 5  | 39  | 2   | 42  |
| II               | 31 | 34  | 23  | 42  |
| III              | 38 | 17  | 36  | 19  |
|                  | DS |     | 0.087 | 0.783 |
| I                | 1  | 1   | 1   | 1   |
| II               | 7  | 20  | 9   | 19  |
| III              | 66 | 70  | 51  | 83  |
|                  | GPT|     | 0.657 | 0.985 |
| ≤.9              | 71 | 85  | 58  | 98  |
| 40               | 3  | 5   | 3   | 5   |
|                  | GOT|     | 0.510 | 0.617 |
| ≤.6              | 67 | 84  | 57  | 94  |
| 40               | 7  | 6   | 4   | 9   |
|                  | CRP|     | 0.704 | 0.880 |
| ≤.8              | 53 | 62  | 42  | 83  |
| 10               | 21 | 28  | 19  | 20  |
|                  | A/G|     | 0.916 | 0.041 |
| ≤.04             | 29 | 36  | 18  | 47  |
| 0.5              | 45 | 54  | 43  | 56  |
|                  | LDH|     | 0.215 | 0.530 |
| ≤.53             | 54 | 73  | 46  | 82  |
| ≥245             | 20 | 17  | 15  | 21  |
| Del(17p)         | 3  | 0   | 0.028 | 3   | 0   | 0.028 |
| T (6;14)         | 3  | 3   | 1.000 | 2   | 4   | 0.405 |
| T(11;14)         | 2  | 2   | 1.000 | 1   | 3   | 0.615 |
| T (14;16)        | 5  | 1   | 0.134 | 5   | 1   | 0.134 |
| T (14;20)        | 3  | 0   | 0.028 | 2   | 1   | 1.000 |
| T(4;14)          | 13 | 3   | 0.002 | 9   | 7   | 0.608 |
| PLATELET count   |    | 0.000 | 0.000 |
| ≥000             | 55 | 88  | 45  | 98  |
| 100              | 19 | 2   | 16  | 5   |
| Herpes           | 13 | 19  | 0.569 | 9   | 23  |
| Maintenance      |    | 0.087 | 0.737 |
| No               | 13 | 7   | 10  | 10  |
| Thalidomide      | 48 | 63  | 37  | 74  |
| Lenalidomide     | 13 | 19  | 14  | 18  |
| Bortezomib       | 0  | 1   | 0   | 1   |
| Prognostic factors | PFS HR(95% CI) | P | OS HR(95% CI) | P |
|--------------------|----------------|---|----------------|---|
| Age (years)        | 1.051(1.031-1.071) | 0.000 | 1.034(1.012-1.055) | 0.002 |
| Gender             | 1.265(0.828-1.931) | 0.277 | 1.412(0.926-2.152) | 0.109 |
| Classification     | 1.037(0.949-1.132) | 1.037 | 1.093(0.999-1.196) | 0.053 |
| ISS stage          | 1.718(1.247-2.366) | 0.001 | 2.093(1.520-2.883) | 0.000 |
| DS stage           | 2.094(1.084-4.054) | 0.028 | 1.982(1.015-3.869) | 0.045 |
| GPT                | 1.011(1.002-1.021) | 0.019 | 1.009(0.999-1.019) | 0.082 |
| GOT                | 1.022(1.011-1.033) | 0.000 | 1.025(1.013-1.038) | 0.000 |
| CRP                | 1.002(0.996-1.007) | 0.593 | 1.002(0.996-1.008) | 0.491 |
| A/G                | 1.041(0.698-1.553) | 0.844 | 1.149(0.754-1.751) | 0.518 |
| LDH                | 1.003(1.001-1.004) | 0.000 | 1.003(1.002-1.005) | 0.000 |
| Del(17p)           | 58.843(13.580-254.969) | 0.000 | 11.329(3.419-37.541) | 0.000 |
| T(6;14)            | 1.021(0.319-3.266) | 0.972 | 1.285(0.399-4.134) | 0.674 |
|                | Coefficient (95% CI) | p-value | Coefficient (95% CI) | p-value |
|----------------|----------------------|---------|----------------------|---------|
| **T(11;14)**   | 1.149 (0.281-4.708)  | 0.847   | 1.188 (0.290-4.871)  | 0.811   |
| **T(14;16)**   | 7.152 (3.157-16.202) | 0.000   | 9.542 (4.072-22.359) | 0.000   |
| **T(14;20)**   | 6.442 (1.994-20.815) | 0.002   | 11.912 (3.477-40.809) | 0.000   |
| **T(4;14)**    | 4.370 (2.143-8.914)  | 0.000   | 7.330 (3.464-15.509) | 0.000   |
| **PLATELET count** | 9.604 (4.965-18.578) | 0.000   | 8.437 (4.528-15.721) | 0.000   |
| **Herpes**     | 0.821 (0.451-1.495)  | 0.52    | 0.908 (0.498-1.653)  | 0.751   |
| **Maintenance** | 0.578 (0.344-0.971)  | 0.038   | 0.593 (0.334-1.056)  | 0.076   |
| **Chemotherapy regimen** | 1.005 (0.856-1.180) | 0.952   | 0.949 (0.795-1.133)  | 0.564   |
| **Autotransplantation** | 0.339 (0.137-0.842) | 0.020   | 0.347 (0.140-0.860)  | 0.022   |
| **TC**         | 0.773 (0.631-0.947)  | 0.013   | 0.757 (0.617-0.927)  | 0.007   |
| **TG**         | 0.861 (0.666-1.114)  | 0.255   | 0.846 (0.642-1.113)  | 0.232   |
| **P**          | 1.143 (0.953-1.370)  | 0.15    | 1.113 (0.934-1.325)  | 0.232   |
| **C1 reduction rate** | 0.412 (0.325-0.521) | 0.000   | 0.438 (0.346-0.554)  | 0.000   |
| **C2 reduction rate** | 0.412 (0.325-0.523) | 0.000   | 0.441 (0.351-0.553)  | 0.000   |
| **C3 reduction rate** | 0.390 (0.303-0.501) | 0.000   | 0.377 (0.290-0.490)  | 0.000   |
| **C4 reduction rate** | 0.358 (0.283-0.455) | 0.000   | 0.345 (0.267-0.445)  | 0.000   |

Table 3. Multivariate analysis of PFS.
| Prognostic factors          | HR(95% CI)          | P       |
|----------------------------|---------------------|---------|
| Age                        | 1.059(1.033-1.085)  | 0.000   |
| ISS stage                  | 2.136(1.500-3.041)  | 0.000   |
| DS stage                   | 1.622(0.264-1.622)  | 0.264   |
| GPT                        | 1.017(0.997-1.036)  | 0.097   |
| GOT                        | 1.002(0.977-1.028)  | 0.857   |
| LDH                        | 1.000(0.997-1.003)  | 0.944   |
| Del(17p)                   | 20.598(3.570-118.848) | 0.001  |
| T(14;16)                   | 3.914(1.180-12.978) | 0.026   |
| T(14;20)                   | 13.988(2.438-80.385) | 0.003  |
| T(4;14)                    | 1.414(0.562-3.558)  | 0.462   |
| PLATELET count             | 1.880(0.732-4.830)  | 0.189   |
| Maintenance                | 0.410(0.236-0.710)  | 0.001   |
| Autotransplantation        | 0.201(0.069-0.583)  | 0.003   |
| TC                         | 0.689(0.533-0.891)  | 0.005   |
| C1 reduction rate          | 0.474(0.293-0.767)  | 0.002   |
| C2 reduction rate          | 0.792(0.440-1.427)  | 0.438   |
| C3 reduction rate          | 1.974(0.921-4.230)  | 0.080   |
| C4 reduction rate          | 0.254(0.139-0.463)  | 0.000   |

Table 4. Multivariate analysis of OS.
| Prognostic factors     | HR(95% CI)       | P    |
|------------------------|------------------|------|
| ISS stage              | 1.879(1.315-2.686) | 0.001|
| Age                    | 1.054(1.027-1.081) | 0.024|
| DS stage               | 1.829(0.791-4.233) | 0.158|
| GOT                    | 1.009(0.988-1.031) | 0.395|
| LDH                    | 0.998(0.996-1.001) | 0.264|
| Del(17p)               | 6.527(1.095-38.893) | 0.039|
| T(14;16)               | 4.874(1.344-17.684) | 0.016|
| T(14;20)               | 30.719(4.811-196.154) | 0.000|
| T(4;14)                | 4.478(1.814-11.061) | 0.001|
| Platelet count         | 2.929(1.269-6.756) | 0.012|
| Autotransplantation    | 0.211(0.069-0.647) | 0.006|
| TC                     | 0.735(0.573-0.943) | 0.016|
| C1 reduction rate      | 0.868(0.543-1.387) | 0.553|
| C2 reduction rate      | 0.680(0.386-1.197) | 0.181|
| C3 reduction rate      | 1.055(0.592-1.879) | 0.856|
| C4 reduction rate      | 0.608(0.350-1.058) | 0.078|

Figures
Figure 1

The K–M curve and the log-rank tests about PFS between the different reduction rate of M protein after first cycle chemotherapy (P<0.001)

Figure 2

The K–M curve and the log-rank tests about PFS between the different reduction rate of M protein after fourth cycle chemotherapy (P<0.001)

Supplementary Files

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Declarations file.png