Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

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

JunYu Zhang
Lishui Municipal Central Hospital
Linjie Li (lilinjie0394@163.com)
Lishui Municipal Central Hospital
WeiE Liu
Lishui Municipal Central Hospital
MinLei Zhao
Lishui Municipal Central Hospital
YangJin Jin
Lishui Municipal Central Hospital
Yu Chen
Lishui Municipal Central Hospital
NengWen Xu
Lishui Municipal Central Hospital
CangJian Zhang
Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Research article

Keywords: Multiple myeloma, progression-free survival, reduction rate of M protein, first chemotherapy, fourth chemotherapy

Posted Date: January 29th, 2020

DOI: https://doi.org/10.21203/rs.2.22217/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

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 (C1reduction 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 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 24 h 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 24 h 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 48.4months (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: 0474, 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, adriamycinc, dexamethasone, TCD thalidomide cyclophosphamide, dexamethasone, PD bortezomib, dexamethasone, TC total cholesterol, TG triglyeride, 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

Funding: Not applicable

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.

Acknowledgements: Not applicable

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7-30.
2. Rajkumar SV, Kumar S: Multiple myeloma: diagnosis and treatment . Mayo Clin Proc. 2016, 91:101-119.
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc. 2003;78(1):21–33.
4. Fonseca R, Bergsagel PL, Drach J, et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. Leukemia. 2009;23(12):2210-2221.
5. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood. 2007;109(8):3489-3495.
6. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. Mayo Clin Proc. 2007;82(3):323–341.

7. Stewart AK, Bergsagel PL, Greipp PR, et al. A practical guide to defining high-risk myeloma for clinical trials, patient counseling and choice of therapy. Leukemia.2007;21(3):529–534.
8. Rajkumar SV. Multiple myeloma: 2012 update on diagnosis, risk-stratification, and management. Am J Hematol. 2012;87(1):78–88.
9. Avet-Loiseau H, Hulin C, Campion L, et al. Chromosomal abnormalities are major prognostic factors in elderly patients with multiple myeloma: the intergroupe francophone du myélome experience. J Clin Oncol Off J Am Soc Clin Oncol.2013;31(22):2806–2809.
10. Palumbo, A. et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood 125, 2068–2074 (2015).
11. Gutierrez, N. C. et al. Prognostic and biological implications of genetic abnormalities in multiple myeloma undergoing autologous stem cell transplantation: t(4;14) is the most relevant adverse prognostic factor, whereas RB deletion as a unique abnormality is not associated with adverse prognosis. Leukemia 21, 143–150 (2007).
12. Palumbo, A. et al. Revised International Staging System for multiple myeloma: a report from International Myeloma Working Group. J. Clin. Oncol. 33, 2863–2869 (2015).
13. Greipp, P. R.,J. S. Miguel, B. G. M. Dune et al. International Staging System for multiple myeloma. J. Clin. Oncol. 23, 3412–3420 (2005).
14. Ludwig, H. et al. Myeloma in patients younger than age 50 years presents with more favorable features and shows better survival: an analysis of 10 549 patients from the International Myeloma Working Group. Blood 111, 4039–4047 (2008).
15. Stella-Holowiecka, B. et al. Beta-2-microglobulin level predicts outcome following autologous hematopoietic stem cell transplantation in patients with multiple myeloma. Transplant. Proc. 39, 2893–2897 (2007).
16. Palumbo A, Anderson K: Multiple myeloma. N Engl J Med. 2011, 364:1046-1060.
17. Kumar SK, Rajkumar SV. The multiple my elomas - current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol. 2018;15(7): 409-421.
18. Sethi S,Fervenza FC,Rajkumar SV.Spectrum of manifestations of monoclonal gammopathy-associated renal lesions.Curr Opin Nephrol Hypertens, 2016; 25(2): 127-137.
19. Niels W.C.J. van de Donk, Antonio Palumbo, Hans Erik Johnsen, et al. The clinical relevance and management of monoclonal gammopathy of undetermined significance and related disorders: recommendations from the European Myeloma Network. Haematologica. 2014 Jun; 99(6): 984–996.doi: 3324/haematol.2013.100552
20. González-Calle V1, Dávila J1, Escalante F et al. Bence Jones proteinuria in smoldering multiple myeloma as a predictor marker of progression to symptomatic multiple myeloma. 2016; 30(10): 2026-2031.
21. Jo Caers, Carlos Fernández de Larrea, Xavier Leleu, et al. The Changing Landscape of Smoldering Multiple Myeloma: A European Perspective. Oncologist. 2016 Mar; 21(3): 333–342.doi: 1634/theoncologist.2015-0303

22. Fernandez de, Larrea C, et al. Evolving M-protein pattern in patients with smoldering multiple myeloma: impacton on early progression. 2018;32:1427–1434. doi: 10.1038/s41375-018-0013-4.
23. Susanna Gassiot, Yolanda González, Mireia Morgades et al. Response to First Cycle Is the Major Predictor of Long-Term Response to Lenalidomide and Dexamethasone Therapy in Relapsed and Refractory Multiple Myeloma: Can We Spare Patients the Toxicity and Costs of Additional Agents? Clinical Lymphoma, Myeloma & Leukemia. 2019; 19(9): 585-592
24. Catherine Atkin, Alex Richter, Elizabeth Sapey. What is the significance of monoclonal gammopathy of undetermined significance? Clin Med (Lond). 2018 Oct; 18(5): 391–396.doi: 7861/clinmedicine.18-5-391
25. Arjun Lakshman, Utkarsh Painuly, S. Vincent Rajkumar et al. Impact of acquired del(17p) in multiple myeloma. Blood advances. 2019; 3(13): 1930-1938.
26. Gran C, Uttervall K, Borg Bruchfeld J et al. Translocation (11;14) in newly diagnosed multiple myeloma, time to reclassify this standard risk chromosomal aberraten? Eur J Haematol. 2019; doi: 10.1111/ejh.13325. PMID:31487754
27. Sasaki K1, Lu G, Saliba RM, Bashir Q et al. mpact of t(11;14)(q13;q32) on the outcome of autologous hematopoietic cell transplantation in multiple myeloma. Biol Blood Marrow Transplant. 2013;19(8): 1227-1232.

28. Tian E1, Sawyer JR, Heuck CJ, et al. In multiple myeloma, 14q32 translocations are nonrandom chromosomal fusions driving high expression levels of the respective partner genes. Genes Chromosomes Cancer. 2014; 53(7): 549-57.

29. Ngo BT1, Felthaus J, Hein M et al. Monitoring bortezomib therapy in multiple myeloma: screening of cyclin D1, D2, and D3 via reliable real-time polymerase chain reaction and association with clinico-pathological features and outcome. Leuk Lymphoma. 2010; 51(9): 1632-42.

30. Pellegrino Musto, Vittorio Montefusco. Are maintenance and continuous therapies indicated for Every Patient with Multiple Myeloma? Expert Review of Hematology. DOI:10.1080/17474086.2016.1196127.

31. Fcaon T. Maintenance therapy for multiple myeloma in the era of novel agents. Hematology Am Soc Hematol Educ Program. 2015: 279-85. DOI: 10.1182/asheducation-2015.1.279.

32. Jackson GH, Davies FE, Pawlyn C et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Curr Opin Hematol. 2019 Nov;26(6):386-391. DOI: 10.1097/MOH.0000000000000538.

33. Choi T. Is autologous stem cell transplantation still relevant for multiple myeloma? Current Opinion in Hematology, 2019 09;26(6): 386 – 391. DOI:1097/MOH.0000000000000538
34. Al Hamed R1, Bazarbachi AH1, Malard F1 et al. Current status of autologous stem cell transplantation for multiple myeloma. Blood Cancer J. 2019 Apr 8;9(4):44. doi: 10.1038/s41408-019-

0205-9.

35. Soekojo Cinnie Y, Kumar Shaji K. Stem-cell transplantation in multiple myeloma: how far have we come? Therapeutic Advances in Hematology: 2019; 10; 204062071988811. DOI:1177/2040620719888111

36. MA Congcong, Liu Yanqin. Changes of blood lipid levels in patients withmultiplemyeloma and its clinical significance. ShiYongLinChuangYiYao magazine. 2014, 18(7):113-115.

37. Jafri H, Alsheikh-Ali A A, Karas R H. Baseline and on-treatment high-density lipoprotein cholesterol and the risk of cancer in randomized controlled trials of lipid-altering therapy[J]. J Am Coll cardiol, 2010, 55(25): 2846.

38. Kim DS, Yu ES, Kang KW, et al. Myeloma prognostic index at diagnosis might be a prognostic marker in patients newly diagnosed with multiple myeloma. Korean J Intern Med. 2017;32(4):711–721.

39. Rasmus Sørrig, Tobias W. Klausen, Morten Salomo, et al. Immunoparesis in newly diagnosed Multiple Myeloma patients: Effects on overall survival and progression free survival in the Danish population. PLoS One. 2017; 12(12): e0188988. doi: 10.1371/journal.pone.0188988

40. Andriandi, Achmad Fauzi Kamal. Survival rate of multiple myeloma patients in Indonesia: A retrospective study in multiple myeloma at a single institution. Ann Med Surg (Lond). 2019 May; 41: 11–15. doi: 10.1016/j.amsu.2019.03.011

41. Marie-Lorraine Chretien, Benjamin Hebraud, Valérie Cances-Lauwers, et al. Age is a prognostic factor even among patients with multiple myeloma younger than 66 years treated with high-dose melphalan: the IFM experience on 2316 patients. Haematologica. 2014 Jul; 99(7): 1236–1238. doi: 10.3324/haematol.2013.098608

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)			0.000			0.003
<65	25	56		21	60	
≥65	49	34		40	43	
Gender			0.912			0.903
Male	36	43		37	42	
Female	38	47		39	46	
Classification			0.935			0.665
IgG	4	12		1	15	
IgG，κ	19	18		19	18	
IgG，λ	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	
Chemotherapy regimen			0.878			0.022
PCD	27	34		24	37	
PAD	12	16		14	14	
VRD	15	18		18	15	
VAD	17	19		20	16	
TCD	1	0		1	0	
PD	2	3		4	1	
Autotransplantation	5	20	0.006	5	20	0.020
TC			0.903			0.767
5.2mmol/L	63	76		52	86	
≥62mmol/Lp	11	14		9	17	
TG			0.546			0.778
1.71mmol/L	51	58		41	67	
≥771mmol/Ll	23	32		20	36	
P			0.587			0.568
1.07mmol/L	17	24		13	26	
≥607mmol/Ll	57	66		48	77	

Table 2. Univariate analysis of PFS and OS.

	PFS		OS	
Prognostic factors	HR(95% CI)	P	HR(95% CI)	P
Age（year）	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(1.082-4.054)	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
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

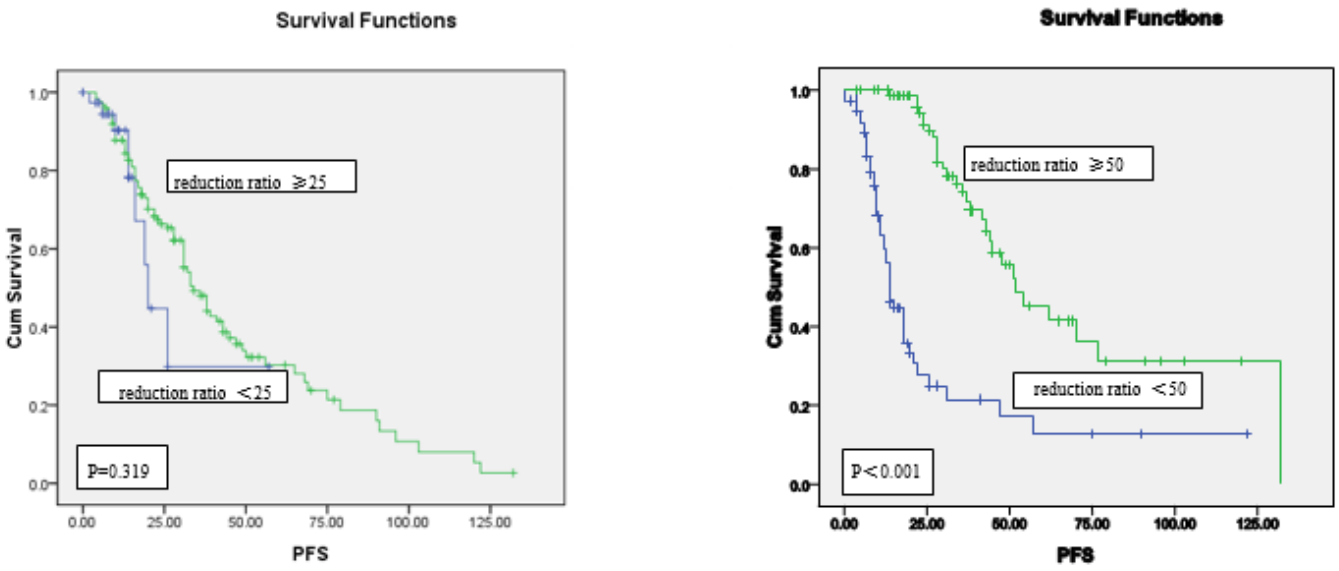


Figure 1

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)

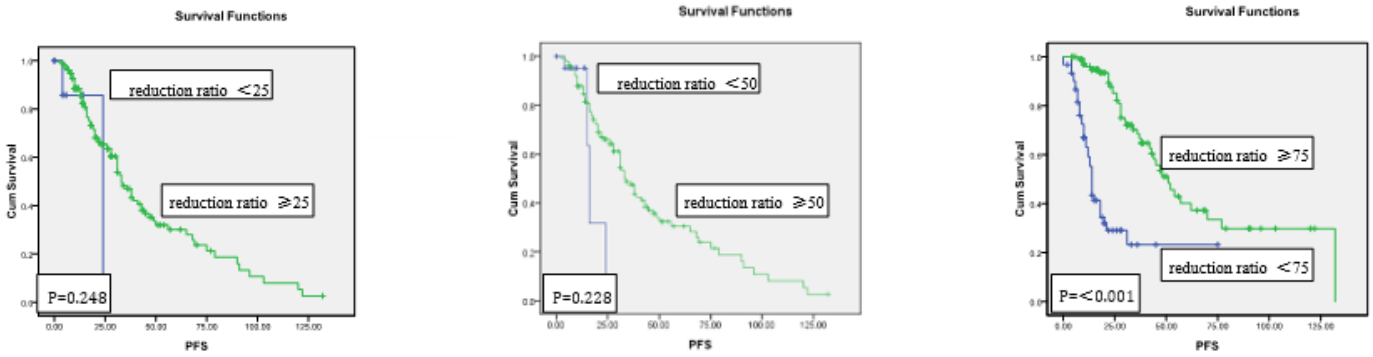


Figure 2

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Declarationsfile.png