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High Levels of Peripheral Blood Circulating Plasma Cells as a Specific Risk Factor for Progression of Smoldering Multiple Myeloma

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Abstract

Smoldering multiple myeloma (SMM) carries a 50% risk of progression to multiple myeloma (MM) or related malignancy within the first 5 years following diagnosis. The goal of this study was to determine if high levels of circulating plasma cells (PCs) are predictive of SMM transformation within the first 2–3 years from diagnosis. Ninety-one patients diagnosed with SMM at Mayo Clinic from January 1994 through January 2007 who had testing for circulating PCs using an immunofluorescent assay and adequate follow up to ascertain disease progression, were studied. High level of circulating PCs was defined as absolute peripheral blood PCs >5000 $\times 10^6$/L and/or > 5% cytoplasmic immunoglobulin (Ig) positive PCs per 100 peripheral blood mononuclear cells. Patients with high circulating PCs (14 of 91 patients, 15%) were significantly more likely to progress to active disease within 2 years compared with patients without high circulating PCs, 71% versus 25%, respectively, P=0.001. Corresponding rates for progression within 3 years were 86% versus 35%, respectively, P<0.001. Overall survival (OS) after both SMM diagnosis and MM diagnosis was also significantly different. High levels of circulating PCs identify SMM patients with an elevated risk of progression within the first 2 to 3 years following diagnosis.

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Authorship Contributions

G.B. and S.V.R. were involved in the concept and design of the study, data collection, data analysis, and wrote the manuscript; R.A.K., D.R.L., T.E.W., S.K., W.G.M., and A.D. were involved with data interpretation, critical review, and critical edits to the manuscript. All authors gave final approval to the manuscript.

Conflicts of Interest Disclosure

The authors declare no conflict of interest.

Keywords

Smoldering multiple myeloma; circulating plasma cells; predictive factor; progression; multiple myeloma

Introduction

Smoldering multiple myeloma (SMM) is an asymptomatic, premalignant condition characterized by monotypic bone marrow plasma cell (PC) infiltration comprising 10% or more of the total cellularity and/or a serum monoclonal immunoglobulin (Ig) of 3 g/dL or more in the absence of end organ damage (CRAB criteria: hyperCalcemia, Renal failure, Anemia, Bone lesions) attributable to PC proliferation.[1–3] In contrast to monoclonal gammopathy of undetermined significance (MGUS) which carries a 1% per year risk of progression to active multiple myeloma (MM), or related plasma cell dyscrasia such as amyloidosis or Waldenström's macroglobulinemia or lymphoma, patients with SMM have a 10% per year risk of transformation.[4] A recent cohort study found that the overall risk of progression in SMM is 10% per year in the first 5 years, but then decreases to 3% per year in the following 5 years, and 1% per year thereafter, suggesting that SMM is a heterogenous clinical entity ranging from biologically aggressive cases most akin to early, active MM, to a more indolent form with a natural history similar to MGUS. Overall, the cumulative probability of progression of SMM at 15 years is over 70%.[5]

Current guidelines recommend close observation and monitoring with no active treatment for patients with SMM.[6] Yet, the paradigm of PC dyscrasia is evolving; with the timing of active therapy for high risk SMM patients recently questioned and early treatment advocated, in an attempt to slow disease progression and possibly prolong survival.[7] Indeed, an interim analysis of a randomized, phase III study evaluating lenalidomide plus dexamethasone versus no treatment for patients with high risk SMM showed prolonged time to progression (TTP) and suggestion of increased overall survival (OS) in the treated arm.[8] This trend was confirmed by a small, phase III, randomized trial evaluating the use of thalidomide plus zolendronic acid (ZA) versus single agent ZA in patients with SMM that showed significantly improved TTP in the active treatment group.[9]

In order to accurately refer patients for early therapy and enrollment in clinical trials, it is critical to identify the subset of SMM patients who will inevitably progress to active MM within the first 2–3 years following diagnosis. Bone marrow PC infiltration over 10%, serum monoclonal protein above 3 g/dL, and abnormal free light chain (FLC) ratio (κ to λ ratio less than 0.125 or more than 8) are recognized as statistically significant predictors of SMM progression to active MM.[10,11] Such risk factors increase the probability of progression from 10% per year in the first 2 years to approximately 20% per year, which is still inadequate in terms of either specificity or positive predictive value (PPV), to use as a rationale for early chemotherapeutic intervention. A long-term goal in the care of SMM patients is to identify risk factors with a PPV nearing or exceeding 90% for disease progression in the first 2–3 years. Circulating monotypic PCs are known to be associated with a worse prognosis in MM.[12] Such studies also suggest that the presence of circulating

PCs is a risk factor for progression in MGUS and SMM.[13,14] However, it is currently unclear what percentage of SMM patients have circulating PCs at diagnosis and whether this finding is of prognostic significance.[15] We hypothesized that above a certain threshold, high levels of circulating PCs are a signature feature of malignant transformation and will therefore be a highly specific, predictive biomarker to identify patients with near 90% probability of developing MM or related malignancy in the first 2–3 years following diagnosis.

Materials and Methods

Study cohort

Review of the Mayo Clinic electronic medical records (EMR) between January 1st 1994 and January 31st 2007 identified 171 patients who were labeled as having SMM and had circulating PC immunofluorescent studies performed prior to disease progression. To this initial cohort the strict diagnostic criteria of International Myeloma Working Group were applied to confirm the diagnosis of SMM: presence of a serum monoclonal Ig level equal or higher than 3 g/dL, and/or bone marrow infiltration with monotypic PCs equal or exceeding 10%, in the absence of PC dyscrasia-related end organ damage (CRAB). Based on this review, we excluded patients who did not meet the strict definition of SMM but rather had MGUS, active MM (according to CRAB criteria), primary amyloidosis or other related PC malignancies; patients who were treated with chemotherapy for hematologic or solid malignancy within the previous 5 years; those with ongoing or recent (less than 5 years) therapy with high dose steroids (more than 15 mg prednisone daily or equivalent), and patients who did not have adequate documented follow up either at Mayo Clinic or elsewhere for at least 48 months following diagnosis. The presence of a second malignancy or myeloproliferative disease did not represent an exclusion criterion, unless patients were actively receiving chemotherapy. After applying the above mentioned exclusion criteria to the initial cohort, 91 patients remained and were studied. This retrospective study was approved by the Mayo Clinic Institutional Review Board and patients were asked to give informed consent to review their medical records for research purposes.

Data collection and endpoints

Mayo Clinic EMR, including demographic data; physician notes; laboratory tests; imaging studies; and pathologic reports such as bone marrow aspirate and biopsy, were reviewed. Relevant laboratory data including circulating PCs, M spike, FLC ratio, hemoglobin, total calcium, creatinine, beta2-microglobulin, Ig subtype quantification, 24 hour urinary protein electrophoresis and immunofixation, bone marrow PC percentage, cytogenetics and fluorescent in situ hybridization (FISH) results were abstracted for analysis.

The method used to quantify circulating PCs in this paper is based on immunofluorescent assay performed on fixed peripheral blood mononucleated cells and required single-slide review by a trained physician. This method was first described by Witzig et al.[14] Patients who underwent quantification of circulating PCs via a different technique (i.e.: flow cytometry) were not included in this study to guarantee consistency and reproducibility of data.

Statistical analysis

The primary study goal was to identify a threshold for circulating PC assay associated with a PPV nearing or exceeding 90% for progression of SMM to MM in the first 2–3 years. The secondary endpoints were evaluation of TTP and OS in patients with high versus low circulating PCs in order to assess the value of this metric in risk stratification of SMM. Two-sided Fisher exact tests were used to test for differences between categorical variables. Two-sided Wilcoxon rank-sum tests were used to compare continuous variables. Survival analysis was done using the Kaplan-Meier method. Differences between survival curves were tested for statistical significance using the 2-sided log-rank test unless otherwise specified. Multivariate analysis was performed using Cox's proportional hazards model. Median follow up time was calculated using the reverse Kaplan-Meier method.

Results

Patient characteristics

Ninety-one patients diagnosed with SMM at Mayo Clinic from January 1994 through January 2007 who also had testing for circulating PCs immunofluorescent assay and adequate follow up to ascertain disease progression were studied. Seventy-five patients (83%) had circulating PCs tested on the same day that bone marrow biopsy was obtained; 9 patients (10%) underwent the test within one month from diagnosis; 5 patients (5%) within 6 months and 2 patients (2%) were tested at 12 months and 14 months from initial diagnosis. These latter two patients remained free from disease progression at long-term follow up. To account for this variability, we verified that no disease progression occurred in the interim time between SMM diagnosis and circulating PC assay and derived TTP using both date of bone marrow biopsy and circulating PC test as starting time. As results were comparable with no change in median time, only the analyses of these subjects as a single group are shown. All patients had bone marrow plasma cell percentage ≥ 10%.

High Circulating PCs and Risk of Progression

The primary scope of studying circulating PCs in SMM patients was to determine whether we could identify a level of peripheral blood disease burden that carries a strong positive predictive value (approaching 90%) for disease progression within 2–3. Our analysis revealed that patients with either an absolute peripheral blood PCs >5000 $\times 10^6$/L and/or >5% cytoplasmic Ig positive PCs per 100 mononuclear cells had a significantly higher likelihood of progression to active disease within 2 years of diagnosis as compared with patients not meeting either criteria (71% versus 25%, respectively, P=0.001). Hence these criteria were used to define high circulating PCs. Fourteen patients in the cohort (15%) were found to have high circulating PCs according to the above mentioned thresholds. Seven of these patients (50%) met high circulating PC criteria according to both absolute and percentage PC count; in five patients (36%) only the percentage of circulating PC exceeded the set cutoff, while two patients (14%) only had an absolute count of PC exceeding the 5000 $\times 10^6$/L threshold.

The threshold of absolute peripheral blood PCs >5000 $\times 10^6$/L and/or >5% cytoplasmic Ig positive PCs per 100 mononuclear cells was selected for testing based on our previous

studies, and the patients identified by this risk factor appear to be unique and non-overlapping with other known risk factors as shown on Table 1.[16] For example, patients with high circulating PCs had lower bone marrow infiltration compared with the low level group (13.5% versus 20%, *P* value 0.07), suggesting that the presence of high circulating cells can not be predicted on the base of high bone marrow disease burden (Table 1).

Since one of our goals was to identify an optimal threshold, we also tested higher levels of circulating PCs to determine if we can improve on the PPV of the test for near inevitable progression in the first 2–3 years. We found that the probability of progression to active malignancy within the first 2 years is improved to 77% by applying a threshold of an absolute peripheral blood PCs >6000 $\times 10^6$/L and/or proportion of cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells >6% (test specificity, 95%). The probability of progression within the same time span increases to 86% in SMM patients (n=7) with absolute peripheral blood PCs >10,000 $\times 10^6$/L and/or proportion of cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells >25% (test specificity, 98%). Taken together, these findings indicate that high level of circulating PCs is a biomarker that identifies SMM patients at a remarkably high risk of progression in the first 2–3 years following diagnosis. The initially identified criteria for high circulating PCs (absolute peripheral blood PCs >5000 $\times 10^6$/L and/or proportion of cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells >5%) remained the best single discriminatory point for identifying SMM patients with an increased risk of early disease progression and was used in the rest of the study for TTP and OS analysis.

Details of progression differences based on high versus low circulating PCs are given in Table 2. Thirteen of 14 patients with high circulating PCs eventually progressed, and MM was the progression event in all these patients. The median TTP was 12 months versus 57 months for those with high and low circulating PCs respectively, P<0.001 (Figure 1). All patients in this study had bone marrow plasma cell percentage ≥ 10%, one of the known risk factors for progression in SMM. We looked at the prognostic value of circulating PC after adjusting for size of the serum M protein, the other known risk factor for progression. Patients with high level circulating PCs had a significantly higher risk of progression to MM compared with patients with low level circulating PCs independent of the size of the M protein, hazard ratio 5.0, (95% CI 2.5–9.5) P<0.001 (Table 3). Of note, the median TTP for patients with a monoclonal component exceeding 3 g/dL was 30 months, compared to 57 months for patients with an M spike less than 3 g/dL, (Figure 2, *P* value 0.01). The prognostic value of circulating PCs for TTP remained significantly different (P<0.001) after adjusting for age, the only variable that was significantly different at baseline between the high and low circulating PCs groups.

Circulating PCs as a component of a risk stratification strategy for SMM

On the basis of our data, we tested whether high circulating PCs could be integrated into a risk stratification model to predict evolution of SMM into MM. A model based uniquely on M spike level exceeding 3 g/dL and high circulating PCs was powerful in discriminating patients according to the likelihood of progression to active disease (Figure 3). Patients with no risk factors had a median TTP of 65 months compared with 30 months for patients with

only one risk factor, and 12 months if both risk factors were present, P <0.001. These differences translated in a relative risk of progression to MM or a related malignancy 2.2 times higher for patients with one risk factor, and 14 times higher for SMM patients presenting with both high M spike and circulating PCs, when compared with individuals presenting with no risk factors.

High Circulating PCs and Overall Survival

Patients with SMM presenting with high level of circulating PCs had significantly poor overall survival (OS) compared with patients who did not have high circulating PCs, 49 months versus 148 months, P<0.001 with an hazard ratio of 5.9 (95% CI, 2.7–12.8) (Figure 4A). Corresponding OS differences from MM diagnosis were 31 months versus 66 months, respectively, P = 0.02 (Figure 4B). OS differences remained significant after adjusting for baseline age differences between the two groups, both for survival from SMM (P<0.001) and from MM diagnosis (P=0.03).

Discussion

SMM is a premalignant condition with an overall risk of progression to MM or a related PC cancer of 70% over 15 years. Rather than a unique disease, SMM is a heterogeneous entity created primarily for clinical purposes to identify patients with asymptomatic plasma cell disorders that have a much higher risk of progression than MGUS (10% versus 1% per year, respectively), and therefore need close follow up.[17,18] From a biologic standpoint, the SMM category includes patients with premalignancy (biological MGUS) as well as those with early, active MM, but there are currently no cellular characteristics that can reliably differentiate the two groups.

Historically, patients with SMM have been observed without therapy because of limited therapeutic options, lack of data from randomized controlled trials, and in consideration of the fact that a proportion of patients can remain progression free for many years. This watchful waiting approach has a number of drawbacks. First, it delays treatment for the 20% of SMM patients who are destined to progress within the first two years, increasing the risk of morbidity and potentially irreversible end organ damage. Second, our prior studies show that it is usually not practical or possible to identify the transformation to MM in a timely manner and intervene before serious end organ damage occurs, as most progression events (even in MGUS) occur in the interval between visits.[19] Third, as our treatment options improve, we and others have hypothesized that one of the reasons MM is traditionally considered incurable is the fact that we have not been able to intervene at the early stages of disease, but have rather waited until the development of end organ damage, such as lytic bone lesions or renal failure, in order to initiate therapy.[20] These concerns all illustrate the need to identify risk factors for early progression of SMM to allow for prompt therapeutic intervention in those who may benefit. Recent studies have shown that one can increase the probability of progression from 10% per year to approximately 20–25% per year using simple biomarkers such as M spike exceeding 3 g/dL in conjunction with bone marrow infiltration above 10%, and abnormal serum FLC ratio <0.125 or >8.0.[10,11] Although these parameters are useful for counseling patients, they do not rise to a threshold in which

immediate therapy can be justified in the absence of end organ damage. We need to identify biomarkers that are predictive with an accuracy exceeding 90% of progression in the first 2 years following diagnosis of SMM in order to be able to consider therapy. Only one such factor has been identified so far: bone marrow plasma cells of 60% or higher.[21] Nevertheless, this risk factor is present in less than 5% of patients with SMM.

Circulating monoclonal PCs is a known prognostic factor in newly diagnosed MM, SMM, and MGUS.[15,22] In an earlier smaller study we had found that increased proliferative rate of circulating PCs and/or numbers of circulating plasma cells had prognostic value, but estimation of proliferative rate of circulating plasma cells is cumbersome.[15] The purpose of this study was to determine in a new cohort of patients if a high level of circulating plasma cells identifies SMM patients with an almost inevitable risk of progression to MM within the first 2–3 years of diagnosis. We hypothesized that high circulating PC levels was not a feature of premalignancy, but rather was an occurrence more consistent with malignant transformation and the resultant ability of monotypic PCs to migrate away from the supportive bone marrow microenvironment into the systemic circulation. In this perspective we hypothesized that circulating PCs represent a sign of impending transformation to active disease and suggest the presence of radiologically and clinically occult distant disease foci. Our study found that 15% of patients with SMM have high circulating PC levels as defined by an absolute peripheral blood PCs >5000 $\times 10^6$/L and/or >5% cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells. This subset of patients had a significantly shorter TTP compared with patients who did not have high circulating PCs, 12 months versus 57 months, P <0.001, independent of previously established risk factors for disease progression. More importantly, patients with high circulating PCs had a remarkably high risk of progression within the first 2 years following diagnosis, compared to the rest of the cohort, 71% versus 25%, respectively, P=0.001. Corresponding rates for progression within 3 years were 86% versus 35%, respectively, P<0.001. While raising the threshold for defining high circulating PCs further increased the probability of progression, these criteria for high circulating PCs provided clinically useful criteria with high discriminatory power. Overall, these findings are consistent with our initial hypothesis as the OS of SMM patients with high circulating PCs was more in keeping with the OS seen in newly diagnosed MM patients, suggesting that these represented a subset of patients with true PC malignancy despite absence of end organ damage. When we combined this risk factor with the size of the M protein, we were able to construct a powerful risk stratification model (Figure 3).

There are some limitations to this study that need to be considered. The sample size is relatively small since this is a rare plasma cell disorder compared with MM or MGUS, and the technology for accurately measuring circulating PCs has been available only in the last 10–15 years.[23] Furthermore, given the need for extended disease follow up, data acquired from a slide based immunofluorescent method employed in the clinical laboratory for a number of years was analyzed. The clinical laboratory now uses a high power with multiparametric flow cytometric approach for the detection of circulating monotypic PCs that will need to be validated. Furthermore, it remains to be established if the incorporation into our risk stratification model of other recently identified laboratory parameters such as FLC, allows for even more powerful prediction of disease progression in SMM and other plasma cell dyscrasias. Irrespective of methodology, however, this study provides a

compelling biologic case that capacity of abnormal PCs to readily liberate from the bone marrow niche to the peripheral blood is a distinct feature of malignant transformation that has already occurred or is imminent. Additional studies to further evaluate the peripheral blood PCs using newer, more readily applicable modalities and assessment of other potential biomarkers such as abnormal immunophenotype, cytogenetic abnormalities, PC proliferative rate etc. should be pursued in association with ongoing clinical trials to best determine how to identify and treat SMM patients with high risk of early disease progression.

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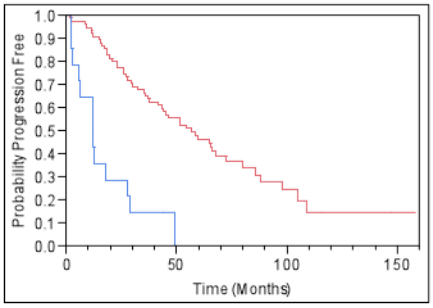
References

1. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003; 121:749–757. [PubMed: 12780789]
2. Bianchi G, Ghobrial IM. Does My Patient with a Serum Monoclonal Spike have Multiple Myeloma? Hematology/oncology clinics of North America. 2012; 26:383–393. [PubMed: 22463833]
3. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2009; 23:3–9.
4. Blade J, Dimopoulos M, Rosinol L, Rajkumar SV, Kyle RA. Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome, and follow-up recommendations. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28:690–697. [PubMed: 20026810]
5. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. The New England journal of medicine. 2007; 356:2582–2590. [PubMed: 17582068]
6. Kyle RA, Buadi F, Rajkumar SV. Management of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). Oncology. 2011; 25:578–586. [PubMed: 21888255]
7. Korde N, Kristinsson SY, Landgren O. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): novel biological insights and development of early treatment strategies. Blood. 2011; 117:5573–5581. [PubMed: 21441462]
8. Detweiler-Short K, Hayman S, Gertz MA, Lacy MQ, Dispenzieri A, Kumar S, et al. Long-term results of single-agent thalidomide as initial therapy for asymptomatic (smoldering or indolent) myeloma. American journal of hematology. 2010; 85:737–740. [PubMed: 20730790]
9. Witzig TE, Mandrekar S, Detweiler-Short K, Lacy MQ, Laumann K, Dispenzieri A, et al. A Phase III Randomized Trial of Thalidomide (THAL) Plus Zoledronic Acid (ZLD) Versus Zoledronic Acid Alone In Patients with Early Stage Multiple Myeloma (MC0289). Blood. 2010; 116:1259–1260.
10. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia : official journal of the Leukemia Society of America, Leukemia Research Fund, UK. 2010; 24:1121–1127.
11. Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood. 2008; 111:785–789. [PubMed: 17942755]

12. Nowakowski GS, Witzig TE, Dingli D, Tracz MJ, Gertz MA, Lacy MQ, et al. Circulating plasma cells detected by flow cytometry as a predictor of survival in 302 patients with newly diagnosed multiple myeloma. Blood. 2005; 106:2276–2279. [PubMed: 15961515]
13. Kumar S, Rajkumar SV, Kyle RA, Lacy MQ, Dispenzieri A, Fonseca R, et al. Prognostic value of circulating plasma cells in monoclonal gammopathy of undetermined significance. J Clin Oncol. 2005; 23:5668–5674. [PubMed: 16110026]
14. Witzig TE, Kyle RA, Greipp PR. Circulating peripheral blood plasma cells in multiple myeloma. Current Topics in Microbiology and Immunology. 1992; 182:195–199. [PubMed: 1490354]
15. Witzig TE, Kyle RA, Ofallon WM, Greipp PR. Detection of Peripheral-Blood Plasma-Cells as a Predictor of Disease Course in Patients with Smoldering Multiple-Myeloma. British journal of haematology. 1994; 87:266–272. [PubMed: 7947266]
16. Witzig TE, Dhodapkar MV, Kyle RA, Greipp PR. Quantitation of circulating peripheral blood plasma cells and their relationship to disease activity in patients with multiple myeloma. Cancer. 1993; 72:108–113. [PubMed: 8508395]
17. Rajkumar SV. Prevention of progression in monoclonal gammopathy of undetermined significance. Clinical cancer research : an official journal of the American Association for Cancer Research. 2009; 15:5606–5608. [PubMed: 19737944]
18. Rajkumar SV. Preventive strategies in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. American journal of hematology. 2012; 87:453–454. [PubMed: 22488611]
19. Bianchi G, Kyle RA, Colby CL, Larson DR, Kumar S, Katzmann JA, et al. Impact of optimal follow-up of monoclonal gammopathy of undetermined significance on early diagnosis and prevention of myeloma-related complications. Blood. 2010; 116:2019–2025. quiz 2197. [PubMed: 20495076]
20. Rajkumar SV. Treatment of multiple myeloma. Nature reviews Clinical oncology. 2011; 8:479–491.
21. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. The New England journal of medicine. 2011; 365:474–475. [PubMed: 21812699]
22. Billadeau D, Van Ness B, Kimlinger T, Kyle RA, Therneau TM, Greipp PR, et al. Clonal circulating cells are common in plasma cell proliferative disorders: a comparison of monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and active myeloma. Blood. 1996; 88:289–296. [PubMed: 8704185]
23. Witzig TE, Gonchoroff NJ, Katzmann JA, Therneau TM, Kyle RA, Greipp PR. Peripheral Blood-B Cell Labeling Indexes Are a Measure of Disease-Activity in Patients with Monoclonal Gammopathies. Journal of Clinical Oncology. 1988; 6:1041–1046. [PubMed: 3286829]

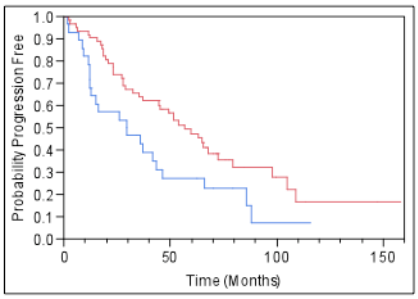


	Median TTP (months)
High circ PC	12
Low circ PC	57

P value: < 0.001

Figure 1. SMM patients with high level of circulating PCs have a significantly shorter time to progression to MM or related neoplasia

Kaplan-Meier curves showing significantly shorter TTP for patients with high level of circulating PCs when compared with patients with low level circulaitng PCs (12 months versus 57 months, respectively) according to the threshold identified in this paper (absolute PCs exceeding 5000 $\times 10^6$/L and/or 5% of cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells).



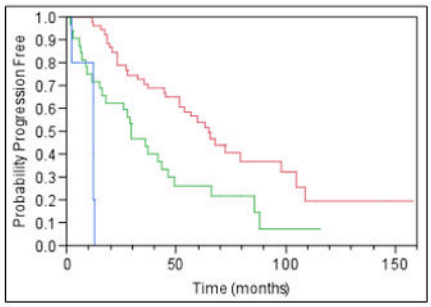
	Median TTP (months)
M spike ≥ 3 g/dL	30
M spike < 3 g/dL	57

Log-rank P value: 0.02

Wilcoxon P value: 0.01

Figure 2. An M spike exceeding 3 g/dL as a risk factor for progression of SMM to active disease

Kaplan-Meier curves illustrating significantly shorter TTP of SMM patients with an M spike equal or above 3 g/dL when compared to patients with monoclonal protein below this threshold.



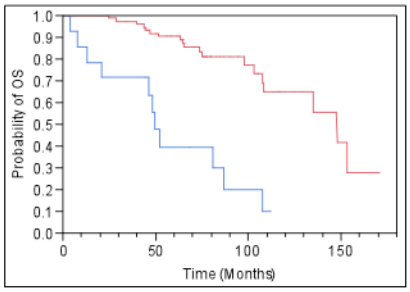
	Median TTP (months)
0 Risk Factor	65
1 Risk Factor	30
2 Risk Factors	12

P value: <0.001

	Patients, N (%)	Relative Risk (95% CI)	*P* value
0 Risk Factor	54 (59)	1	
1 Risk Factor	32 (35)	2.2 (1.3-3.7)	0.004
2 Risk Factors	5 (6)	14 (4.3-41)	<0.001

Figure 3. High level circulating PCs and M spike above 3 g/dL provide a strong predictive model for SMM progression

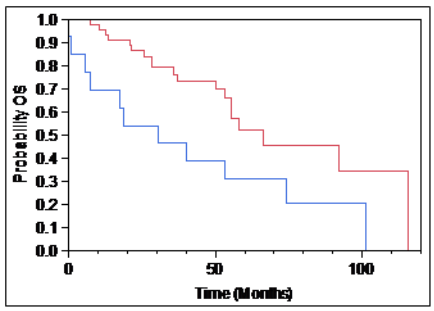
When SMM patients were stratified according to the presence of high circulating PCs and a monoclonal component exceeding 3 g/dL, a strong predictive model for TTP could be derived as shown in this figure. The presence of either one of the two risk factors increased the risk of disease progression by a 2.2 fold. When both risk factors were present, the relative risk of progression was 14 times higher.



	Median OS (months)
High circ PC	49
Low circ PC	148

P value: <0.001

	Patients, N (%)	Relative Risk (95% CI)	*P* value
High circ PC	14 (15)	5.9 (2.7-12.8)	<0.001



	Median OS (months)
High Circ PC	31
Low circ PC	66

Log-Rank P value: 0.02

Wilcoxon P value: 0.002

Figure 4. The presence of high level circulating PCs is a negative prognostic factor for OS from SMM and MM diagnosis

The Kaplan-Meier curve in panel a shows significantly shorter OS from SMM diagnosis for patients with high level of circulating PCs when compared to patients with low level circulating PCs. In SMM patients, the presence of high circulating PCs conferred a 5.9 fold higher risk of demise. The Kaplan-Meier curve in panel b depicts the shorter OS from MM diagnosis for patients with SMM and high level circulating PCs compared to SMM patients with low level circulating PCs.

Table 1

Baseline characteristics of SMM patients with high or low level of circulating PCs

There were no statistically significant differences in the baseline characteristics of the two cohorts of patients with the exception of a higher median age at SMM diagnosis in the high circulating PC group

	Low circulating PCs (n= 77, 85%)	High circulating PCs* (n= 14, 15%)	*P* value
Median age, years (range)	60 (28–82)	69 (52–77)	0.02
Female sex, N (%)	28 (36%)	6 (43%)	0.77
Type of immunoglobulin, N (%)			0.98
IgG	53 (69%)	10 (71%)	
IgA	12 (16%)	4 (29%)	
IgD	1 (1%)	0	
IgM	2 (3%)	0	
Light chain only	4 (5%)	0	
Biclonal	5 (6%)	0	
Median M spike (range), g/dL	2.5 (Undetect-5.4)	2.5 (0.9–4)	0.94
Median bone marrow involvement, %	20 (10–65)	13.5 (10–40)	0.06
Median hemoglobin (range) g/dL	13.4 (11.8–16.7)	13 (12–15)	0.51
Median creatinine (range), mg/dL	1.1 (0.7–1.6)	1.2 (0.9–1.7)	0.28
Median calcium (range), mEq/L	9.4 (8.2–10.6)	9.2 (8.6–10.2)	0.1
Median Beta2 microglobulin (range), mg/dL	2.3 (0.2–4.5)	2.8 (1.5–4.5)	0.07
Median follow up, months	77	112	0.4
Median follo up of living patients, months	75	69	0.5
M spike ≥ 3 g/dL, N (%)	23 (30)	5 (36)	0.76
Hypogammaglobulinemia, N (%)			0.21
0 Ig class	16/72 (22)	0	
1 Ig class	24/72 (33)	3/11 (27)	
2 or more Ig classes	32/72 (45)	8/11 (73)	
Bence Jones proteinuria > 50 mg/24h, N (%)	15/74 (20)	0/12 (0)	0.12

*High circulating plasma cells (PCs) indicates absolute PCs exceeding 5000 $\times 10^6$/L and/or 5% of cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells (high versus low circulating PCs).

Table 2

High level of circulating PCs as a risk factor for rapid progression of SMM to MM

Fourteen out of 91 patients in the cohort (15%) had a circulating PC level exceeding 5000 $\times 10^6$/L and/or 5% of the proportion of cytoplasmic Ig positive PCs per 100 peripheral blood mononuclear cells. These patients had a significantly shorter time to progression to active disease and a significantly higher likelihood of disease transformation within 2–3 years. Three patients in the low circulating PC group had a follow up less than 2 years and were not factored in for the rapid progression analysis, hence a denominator of 74

	Low circulating PCs (N= 77, 85%)	High circulating PCs (N= 14, 15%)	*P* value
Median TTP, (months)	57	12	<0.001
TTP ≤ 2 years, N (%)	18/74 (24)	10/14 (71)	0.001
TTP ≤ 3 years, N (%)	25/74 (34)	12/14 (86)	<0.001

Table 3

High level of circulating PCs is a highly specific test for rapid transformation of SMM to MM

The contingency table shows the relationship between level of circulating PCs (high versus low) and the progression within 3 years from SMM diagnosis (TTP more or less than 3 years). The 5000 $\times 10^6$/L and/or 5% circulating PCs threshold showed a specificity of 96%, with a positive predictive value of 86%

	TTP > 3 years	TTP < 3 years	
Low circulating PCs	48	25	73
High circulating PCs	2	12	14
	50	37	87

Table 4

High circulating PCs is a strong, independent risk factor of SMM transformation

The presence of high circulating PCs at the time of SMM diagnosis confers a 5 times higher risk of progression to active neoplasia, independently from the presence of other established risk factors for disease transformation. An M spike exceeding 3 g/dL gives a 1.8 times higher risk of developing active MM or a related PC dyscrasia

	Patients, N (%)	Relative Risk (95% CI)	*P* value
High circ PCs	14 (15)	5 (2.5–9.5)	<0.001
M spike ≥ 3 g/dL	28 (31)	1.8 (1.1–3)	0.03