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Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients

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Abstract

Therapy for multiple myeloma (MM) has dramatically changed in the past decade with introduction of new drugs, but it is not clear if the improvements have been sustained. We studied 1038 patients diagnosed between 2001 and 2010, grouping patients into two five-year periods by diagnosis, 2001–2005 and 2006–2010. The median estimated follow up for the cohort was 5.9 years with 47% alive at last follow up. The median overall survival (OS) for the entire cohort was 5.2 years; 4.6 years for patients in the 2001–2005 group compared with 6.1 years for the 2006–2010 cohort (P=0.002). The improvement was primarily seen among patients over 65 years; the 6-year OS improving from 31% to 56%; P<0.001. Only 10% of patients died during the first year in the latter group, compared with 17% in the earlier cohort (P<0.01), suggesting improvement in early mortality. The improved outcomes were linked closely to use of one or more new agents in initial therapy. The current results confirm continued survival improvement in MM and highlight the impact of initial therapy with novel agents. Most importantly, we demonstrate that the improved survival is benefitting older patients and that early mortality in this disease has reduced considerably.

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AUTHOR CONTRIBUTIONS

SKK was involved in design of concept, data collection, analysis, and writing the paper, AD, MQL, SRH, SRZ, FKB, NL, RAK, SVR, SP, PK, DD, SJR, JL, AM and MAG were involved in writing the manuscript.

DISCLOSURES

No disclosures relevant to the current manuscript

SUPPLEMENTARY MATERIAL

Supplementary information is available at leukemia's website

Keywords

multiple myeloma; survival; IMiDs; proteasome inhibitors

INTRODUCTION

The treatment paradigms and outcomes for patients with multiple myeloma (MM) have dramatically changed in the past decade with introduction of several new, more effective, and less toxic therapies and more than doubling of the survival. [1–3] Several studies toward the end of the last decade showed an improved survival compared to a nearly stagnant survival during the preceding three decades, where the treatment regimens primarily consisted of alkylating agents, anthracyclines and corticosteroids. [4, 5] During the past decade we have continued to make a remarkable progress in our understanding of the disease biology as well as development of newer therapies, as a result of which we have been able to develop better risk stratification models and risk adapted treatment approaches.[6–18] It is not clear if the trend of improving survival seen in the earlier part of last decade has continued as a result of these more recent advances. Furthermore, the previously described improvements in survival was primarily restricted to the younger patients, with the older patients having derived less benefit from the advances, likely a reflection of lower utilization of stem cell transplantation and reduced access to clinical trials evaluating new drugs.[5] As drugs are approved and become available outside of clinical trials, and treating physicians become more comfortable with using these new drugs, older patients are more likely to receive such agents. Finally, it is not clear if the prognostic factors identified in the era of older drugs are still of value in the current era with the new drugs with new methods of action. We designed the study with the specific goal of examining if the survival improvement witnessed in myeloma is a sustained phenomenon, particularly in the older patients, and to evaluate the commonly recognized risk factors in the context of the newer therapies.

PATIENTS and METHODS

The study included 1038 patients who were started on therapy for symptomatic multiple myeloma during a 10-year period between January 1, 2001 and December 31, 2010 and seen at Mayo Clinic within 30 days of their diagnosis of symptomatic disease. Patients who had an organ involvement with AL amyloidosis at the time of diagnosis were excluded from the current analysis. Data regarding these patients were extracted from prospectively maintained databases and review of medical records. Follow-up information on these patients are collected prospectively and entered at the time of each visit. For patients followed up at other institutions, annual follow-up letters are sent to patients to inquire regarding their disease status. All patients had consented to the use of their medical records and the study was conducted in accordance with the institutional guidelines with approval of the Institutional Review Board and in accordance with the principles of the Helsinki Declaration.

Fluorescent *in-situ* hybridization (FISH) results were considered for analysis only if it was performed within 6 months of diagnosis or prior to the diagnosis of symptomatic myeloma. Tests with insufficient plasma cells for adequate analysis were not included in the analysis. FISH analysis was performed as previously described using the following probes 3cen (D3Z1), 7cen (D7Z1), 9cen (D9Z1), 15cen (D15Z4), 11q13 (CCND1-XT), 14q32 (IGH-XT), 13q14 (RB1), 13q34 (LAMP1), 14q32 (5′IGH,3′IGH), 17p13.1 (p53), and 17cen (D17Z1).[19] The specificity of the detection process is improved with immune-fluorescent detection of the cytoplasmic-immunoglobulin light-chain in the plasma cells as previously described (cIg-FISH). Patients were considered to have high risk disease if FISH studies demonstrated one of the following abnormalities: t(4;14), t(14;16), t(14;20), or loss of p53 gene locus (del 17p or monosomy 17) in the absence of any trisomies. Patients with any of the other abnormalities or a normal FISH were considered to have standard risk multiple myeloma as previously described.[7] Plasma cell labeling index (PCLI; a measure of the plasma cell proliferation) was estimated using a slide-based immunofluorescence method on bone marrow samples, and expressed as the percentage of immunoglobulin positive cells that have taken up bromodeoxyuridine as previously described.[20]

Kaplan-Meier analysis was used for analyzing overall survival, and the differences between the groups were tested for statistical significance using the 2-tailed log-rank test.[21] Survival curves were generated with all patients surviving beyond 6 years censored at that time. Survival estimates and the confidence intervals at different time points were estimated by using the Weibull method. Multivariate analysis of factors affecting survival was carried out using Cox proportional hazards model. Optimal cut points for continuous variables affecting early death were identified by examination of receiver operating characteristic (ROC) analyses. Fisher exact test was used to test differences in nominal variables. Differences in continuous variables between groups were compared using Mann-Whitney or Kruskal-Wallis tests.

RESULTS

The patients were diagnosed between 2001 and 2010, with a median of 106 patients included from each year (range 77 –128). The median age at diagnosis was 66 years (range, 22–93) and 59% were male. Overall, 540 (52%) of the patients were over 65 years and 197 (19%) were over 75 years of age. The median estimated follow up for the entire patient population was 5.9 years (95% CI; 5.5, 6.3) and 53% had died at the time of last follow up. The baseline clinical characteristics are provided in Table 1.

Survival outcomes

The median overall survival from diagnosis for the entire cohort was 5.2 years (95% CI; 4.8, 5.8); the six-year overall survival estimate was 45% (95% CI; 42, 48). The median overall survival of the patients in the more recent group (n=561) was significantly longer compared with the earlier cohort (n=477); 6.1 years (95% CI; 5.0, NR) and 4.6 years (95% CI; 4.1, 5.2), P = 0.002 (Figure 1A). The 6-year overall survival estimates for the earlier cohort was significantly shorter compared with the recent cohorts and were 40% (95% CI; 36, 44) and 51% (95% CI; 46, 56) respectively; P < 0.001. We also examined the trend along the years

using 2-year intervals to examine the consistency in the improvements and as shown in figure 1B; there has been a consistent and steady improvement in survival over the time period studied. Given the limited improvement in survival seen among the older patients in the previous studies[4, 5], we examined if the improved survival was limited to any age group. Notably, there was no survival improvement between the two time periods for patients 65 years and under. The median OS was not reached for either time period among those 65 years and under (Figure 1C; P=NS). In contrast, among patients older than 65 years, the OS of the recent cohort was significantly longer with median of 5 years (95% CI; 4.1, NR) compared with 3.2 years (95% CI; 2.4, 3.8) for the earlier cohort, Figure 1D. We then specifically examined if within the group of patients over 65 years, improved outcomes were noted in the very old (i.e. over 75 years of age) patients as well. Improved survival was seen among patients up to 75 years and those over 75 years of age as well (Supplementary Figures s1A, s1B).

Initial therapy and use of stem cell transplantation

We then examined the impact of novel agents used as part of initial therapy on survival outcomes. The initial treatment regimen contained one or more of the novel drugs (thalidomide, lenalidomide or bortezomib) in 621 (60%) of the patients; a regimen incorporating two novel agents was used in 36 patients (3.5%). Lenalidomide dexamethasone was the most common induction regimen overall with 345 (33%) patients receiving this regimen. The most common non-novel agent regimen used was single agent dexamethasone, with 249 patients receiving this regimen (24%) followed by melphalan and prednisone in 120 patients (12%). The distribution of the most commonly used initial regimens is shown in Table 2. As expected, significantly higher proportion of patients treated in the more recent group had received a novel agent as part of the initial therapy compared with the earlier group (89% vs. 29%; $P < 0.001$). The median OS for patients receiving at least one novel agent as part of the initial therapy was not reached (95% CI; 5.4, NR) compared with 3.8 years (95% CI; 3.2, 4.5) for those not receiving a novel agent as part of initial therapy; $P < 0.001$ (Figure 2A). We then performed a multivariable analysis including the diagnosis period and use of novel agents, and only the use of novel agents was associated with improved survival, suggesting that the improved survival in the recent years is mostly related to the increased use of novel agents as part of initial therapy.

Among the entire cohort, 393 patients (37%) received an autologous stem cell transplant at some point during the disease course, with the median time to transplantation of 5.9 months (range 2 –95). Among patients 65 or younger 277/498 (56%) of patients have undergone an ASCT at the time of last follow up. We did a 6- month landmark analysis to examine the impact of ASCT on overall survival. The median OS for patients receiving an SCT was not reached compared with 4.9 years (95% CI; 4.2, 5.3) for those not receiving an SCT, $P < 0.001$ (Figure 2B). Restricting the analysis to those 65 or younger, the OS was identical for those who have received a SCT so far compared with those who have not yet had a transplant, median not reached for either group (Figure 2C). Among the patients over 65 years 116 (21%) underwent a SCT; the median OS for those undergoing SCT was NR (95% CI; 5.4, NR) compared with 3.1 years (95% CI; 2.5, 3.7) for those who did not, $P <0.01$ (Figure 2D).

Early mortality

Overall, 136 (13%) of the patients died within 1 year of diagnosis with the one-year mortality being significantly lower for the recent group 10% vs. 16% for the older cohort (P = 0.004). The early mortality was significantly lower among the patients who had received one of the newer drugs as part of their initial therapy (8% vs. 19%; P < 0.001). We then examined the factors associated with an early mortality, restricting our analysis to those patients who received a newer agent as part of their initial therapy, as that represents the current practice. ROC curves were generated for the continuous variables to identify the optimal cut point, and the values were rounded for convenience and ease of use. We identified age > 70 years, platelet count < 200×10^6/dL, serum creatinine of > 1.5 mg/dl, serum albumin < 3.5 gm/dL, serum beta 2 microglobulin > 6.5 mg/dL, and LDH > 180 IU/dl as factors associated with early mortality. We first examined all the variables in a multivariable model, and identified age >70, serum albumin < 3.5 gm/dL, and serum beta 2 microglobulin > 6.5 mg/dL as factors independently predicting early mortality. Presence of none, one, two or three factors respectively was associated with a 3%, 5%, 9% or 53% risk of early mortality; P<0.001 (Figure 2E).

Prognostic factors for survival

We then examined the value of previously identified prognostic factors, many of which were identified in the context of older therapies, in this recent cohort of patients. Specifically we examined how the prognostic factors may have changed across the two time periods. We first examined the prognostic value of ISS staging among 916 patients in whom the data was available; the median OS was not reached, 5.7 years and 2.1 years for stages 1, and 2 and 3 in the earlier time period (Figure 3A) compared with NR, NR and was 4.2 years respectively during the second time period (Figure 3B). FISH data from around diagnosis was available for only 50 (10%) patients from the first time period compared with 385 (69%) patients from the more recent time period. The median OS for patients with high-risk FISH (defined as presence of (t(4;14), t(14;16), t(16;20), or del 17p in the absence of any trisomy) or standard-risk FISH were 2.3 years and NR respectively for the earlier time period (P=0.05; Figure 3C) and were 3.5 and NR respectively in the latter time period (P<0.001; Figure 3D). We also examined the prognostic value of FISH based risk status using the traditional definition of high risk FISH, not taking into consideration the overlapping abnormality of trisomies (defined as presence of (t(4;14), t(14;16), t(16;20), or del 17p). The median OS for patients with high-risk FISH or standard-risk FISH were 2.4 years and NR respectively for the earlier time period (P=0.01; Supplementary Figure s2A) and were 5.1 and NR respectively in the latter time period (P=0.046; Supplementary Figure s2B). Next we examined the prognostic value of LDH using a cutoff of 222 IU/dL (upper limit of normal for the laboratory). The median OS for patients with LDH >222 IU/dL and <=222 IU/dL were 1.8 and 5.1 years respectively for the earlier time period (Supplementary Figure s2C) and were 3.0 and NR respectively in the latter time period; P<0.001 for both comparisons (Supplementary Figure s2D). Given the important prognostic value of proliferation in myeloma that has been observed with different methods of assessing proliferation across different studies, we examined the prognostic value of plasma cell labeling index and how it has changed over time. Using the traditional cutoff of 1% for the PCLI, the median OS for patients with PCLI >= 1% and <1% were 3.1 years and 5.3 years respectively for the earlier

time period (P<0.001; Supplementary Figure s3A) and were 5.5 years and NR respectively in the latter time period; (P=NS; Supplementary Figure s3B). However, using a higher cutoff of 3%, the median OS for patients with PCLI >= 3% and <3% were 3.1 years and 5.1 years respectively for the earlier time period (P=0.005; Supplementary Figure s3C) and were 3.8 years and NR respectively in the latter time period; (P=0.001; Supplementary Figure s3D). The relative risks associated with the different prognostic factors during the two time periods are as shown in Table 3.

DISCUSSION

The past few years has witnessed continuing advances in the understanding of the myeloma biology, especially the ability to identify patients with high risk disease based on a variety of techniques such as FISH analysis and gene expression profiling techniques in addition to the traditionally recognized risk factors.[1, 6–10, 22] This improved understanding has been coupled with addition of new therapies, primarily new agents belonging to the IMiD and proteasome inhibitor classes of drugs.[11–18] These improvements have in turn led to better understanding of the differential impact of specific drugs in patients with specific high-risk features such as the use of bortezomib for patients with high-risk translocations and 17p deletion.[23, 24] The current analysis provides evidence supporting continued improvement in the survival outcomes within the past decade with those patients identified in the second half enjoying longer survival, and confirms the continuation of the trend we started seeing in the early part of last decade. What is striking, and very encouraging, is the significant improvement seen among the older patients, a group that was left behind in the early period of improved outcomes. This is likely a reflection of the increased use of the newer drugs among the older patients, as is suggested by the significantly higher proportion of patients in the second half receiving a regimen that contained one of the newer drugs. These results are in concordance with the phase 3 trials that demonstrated improved survival for patients over 65 with the addition of thalidomide or bortezomib to melphalan and prednisone.[25–29] From the current analysis, the dominant driving factor behind the observed improvement appears to be the increased use of the novel agents in the more recent period. However, the lack of a further improvement in survival among the younger patients highlights the need for continued innovation in the treatment approaches, both in terms of introduction of novel drugs with different mechanisms of action compared to the IMiDs and the proteasome inhibitors. The newer derivatives of the IMiD family (pomalidomide) and the next generation proteasome inhibitors (carfilzomib), which have been shown to improve survival among patients who have become refractory to the previous generation of drugs, the improvements have been incremental and limited to a small proportion of patients.[17, 18] A substantial proportion of patients eligible for SCT have received one in this current cohort. While the survival of patients undergoing an SCT is better, as would be expected from the selection bias inherent in being eligible for SCT, two aspects needs to be highlighted. Among the group of patients 65 or younger, the OS was similar between those who had a transplant and those who still have not had one. This reflects our standard approach of collecting stem cells in all eligible patients and giving the patients the option of an early transplant or a delayed one at relapse, given the equivalent results with either approach. This result is consistent with our previous reports.[30] The improved survival among those over 65

years who had undergone SCT reflects the improved outcomes among those with better performance status and lack of significant comorbidities, as they are likely to be considered for a transplant. It also highlights the feasibility and safety of this approach among selected older patients.[31, 32]

Another aspect of the current results that is clearly encouraging is the significant decrease in the early mortality (death within 1 year of diagnosis) in myeloma.[33, 34] The population included in the current study gives a better real-world view of the changes in the early mortality as we included only patients who were seen within 30 days of diagnosis. Even with this criteria, the actual proportion of patients dying early after diagnosis is likely to be higher as many critically sick patients are unlikely to get to a tertiary referral center in a timely fashion. This has to be compared and contrasted with the early mortality figures that have been reported from the phase 3 trials performed during the last decade. While confirming the trend that we are observing here, the figures from phase 3 trials are substantially lower highlighting the skewed nature of patients who are eligible for enrolment in clinical trials. Using the current set of patients, we were able to identify specific factors that increased the risk of early mortality, which in turn can help us develop specific therapeutic approaches in the context of well designed clinical trials for these high risk patients. Similar findings were seen in a French study, albeit in a transplant eligible patient population.[34] It is quite likely that the low albumin, elevated B2M, and age over 70 years reflect the presence of comorbidities that can result in decreased ability to treat the disease in an effective manner compared to the rest of the patients and increase risk of toxicities with the regimens currently used.

The changes in the treatment approaches and the specific mechanisms of the drugs utilized can clearly affect different aspects of the biology in unique ways. So we examined the various prognostic factors that have been described over time to see if they are still applicable in the era of newer therapies and improved overall survival.[7, 22, 35–37] Interestingly, nearly all the prognostic factors continue to identify patients with worse outcomes, with FISH based high-risk stratification remaining a powerful tool for clinical use. One striking finding was the complete lack of prognostic value for the plasma cell labeling index in the newer cohort using the traditional cut off of 1%, a finding we had previously reported in the context of IMiD based therapies.[38, 39] However, using a higher cut off of 3% still appear to identify patients with poor outcomes, and this is likely a reflection of the ability of the newer drugs to abrogate some of the mechanisms of poor prognosis associated with high proliferative rate. It is possible that the inherent lack of sensitivity of this slide based test may not allow adequate discrimination between those with groups with high and low proliferation and a different methodology with more sensitivity and or specificity may still have clinical utility.[20] To this end, the slide-based method is not longer being used at our institution and we have shifted to a flow base method that determines the proportion of cells in the S-phase. This is particularly relevant, as proliferation signatures have been commonly identified as a poor prognostic factor in gene expression based studies in myeloma.[40]

In conclusion, the current results indicate continued improvement in the survival of patients with myeloma, reflecting the impact of improved therapies. It is particularly encouraging to

note the improved outcomes in the elderly patients, and the decrease in the early mortality, both of which likely reflect the use of new drugs that can be administered with less toxicity and achieve a more rapid control of disease at the outset. Finally, identification of high risk characteristics at diagnosis, especially, cytogenetic abnormalities, will allow us to direct our efforts towards the patients currently doing poorly, so that progress can continue to be made.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1A

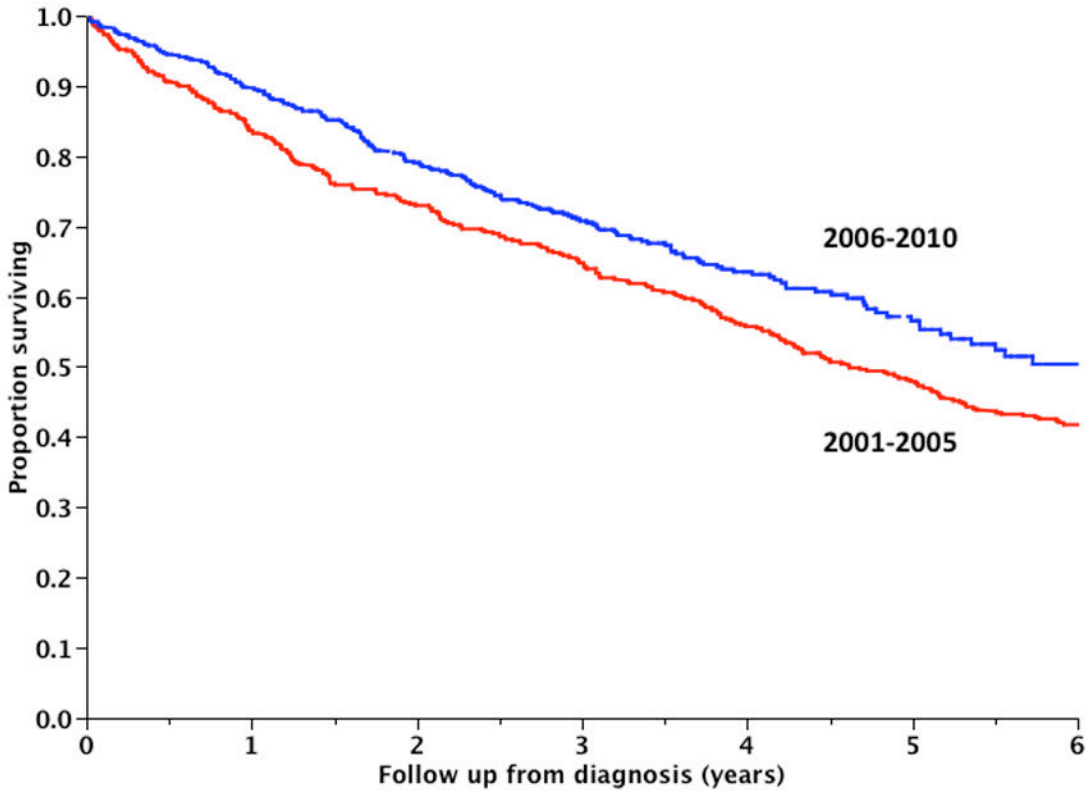


Figure 1B

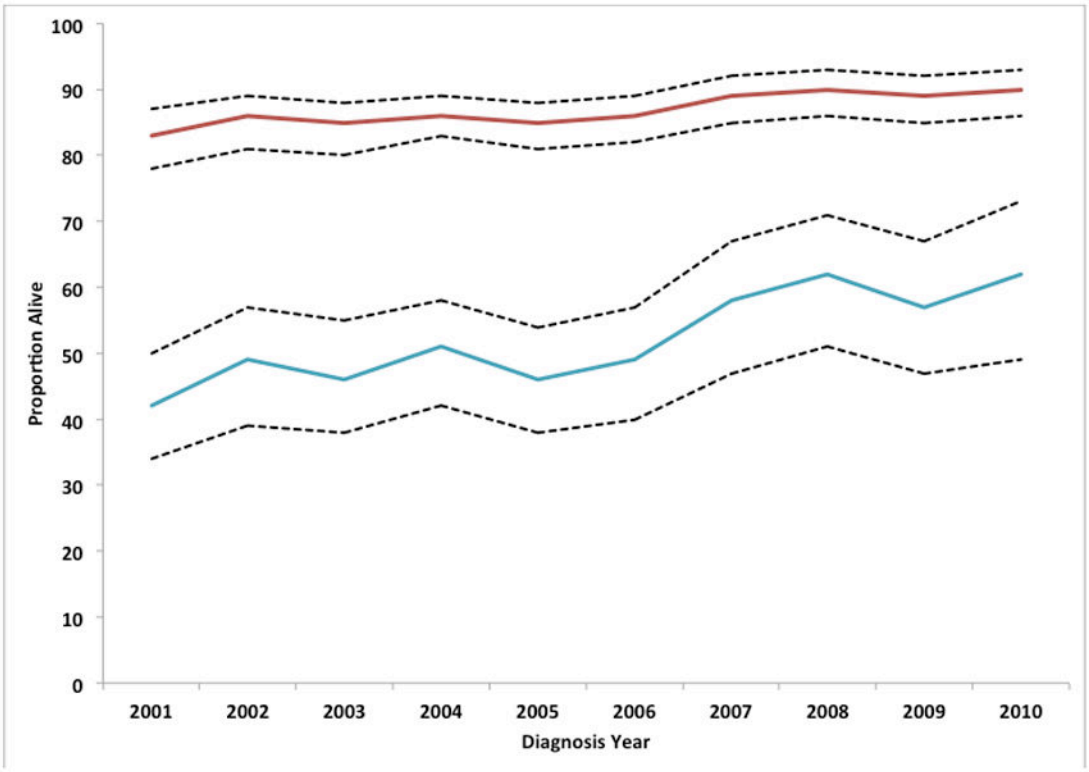
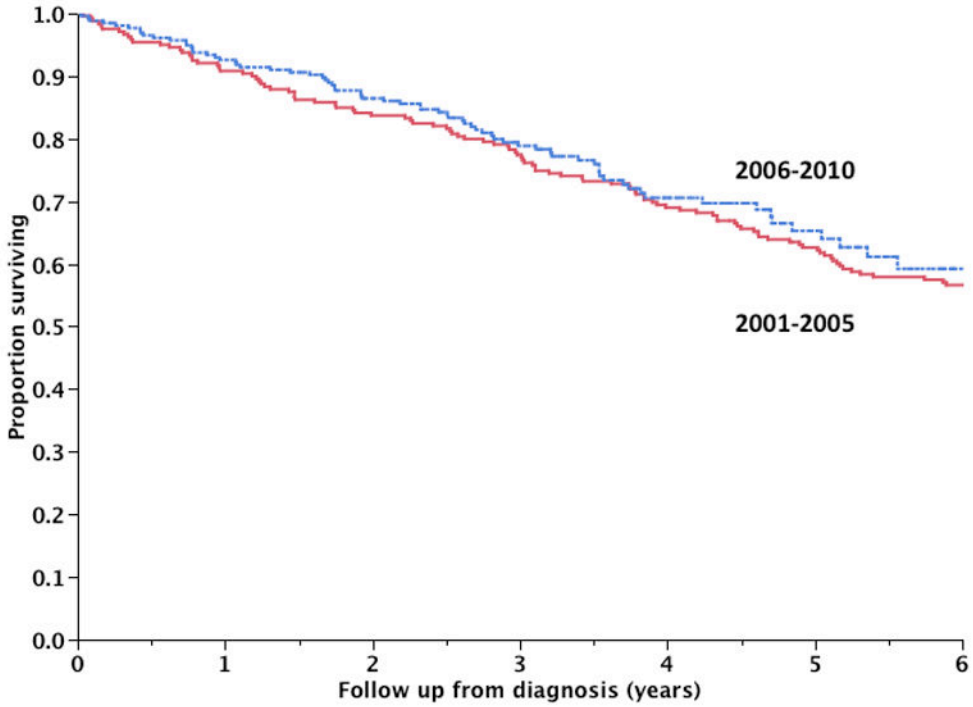


Figure 1C



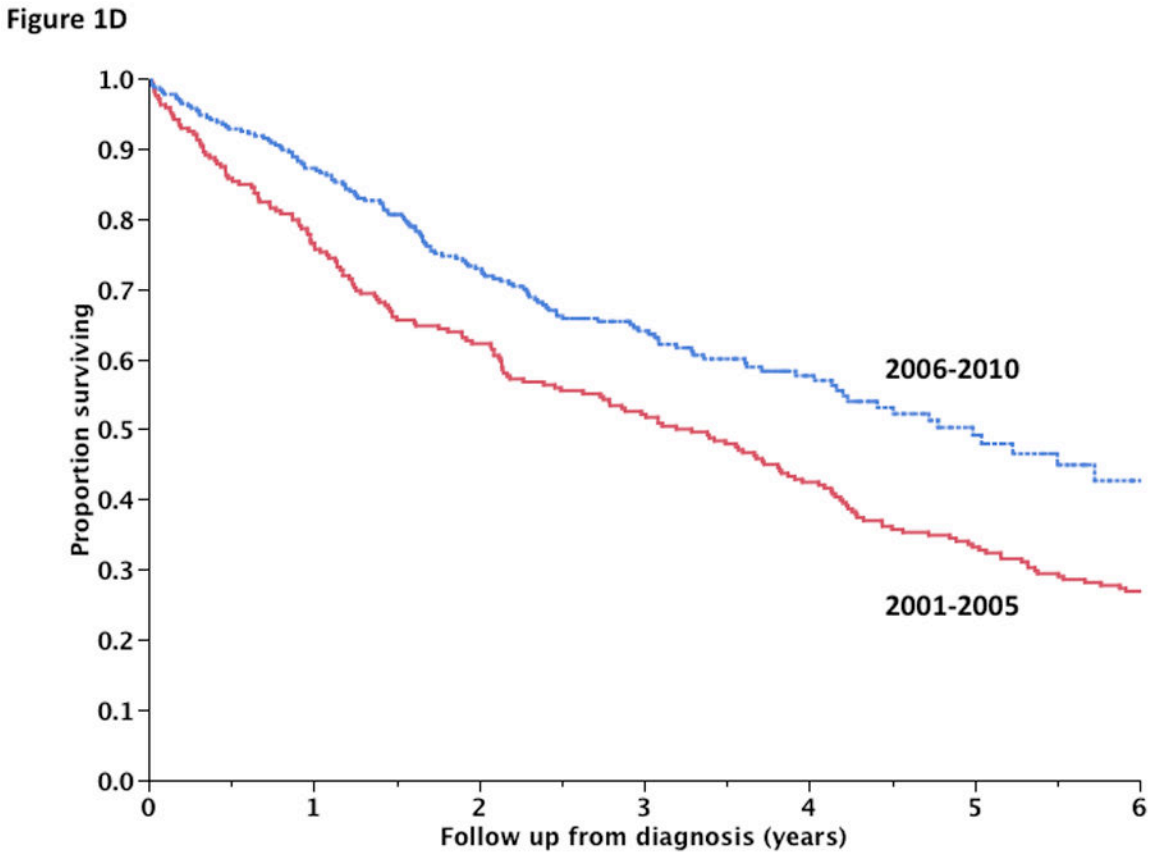
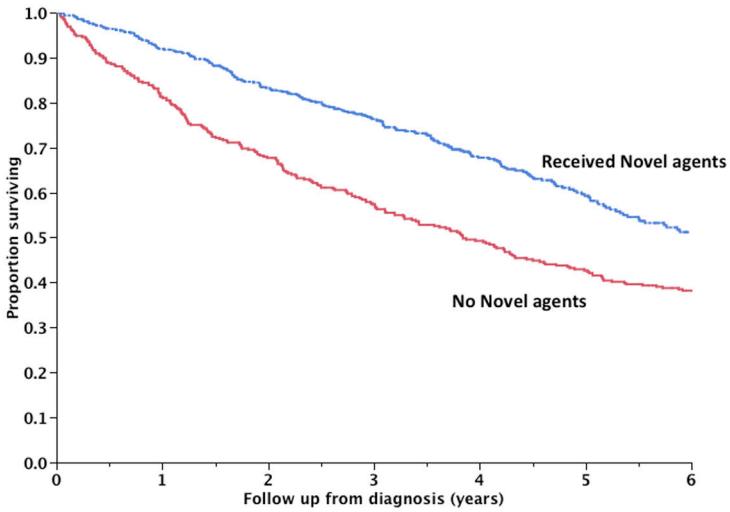


Figure 1.

Panel A shows the overall survival comparison between patients diagnosed during January 2001– December 2005 and those diagnosed during January 2006 and December 2010. ***Panel B*** shows the trends in the 1 and 5 year overall survival estimates between January 2001 and December 2010 with patients grouped by the year of diagnosis. The dotted lines represent the 95% confidence intervals. ***Panel C*** shows the overall survival comparison between patients diagnosed during 2001– 2005 and those diagnosed during 2006–2010 limited to patients 65 years or younger. ***Panel D*** shows the overall survival comparison between patients diagnosed during 2001– 2005 and those diagnosed during 2006–2010 limited to patients older than 65 years.

Figure 2A



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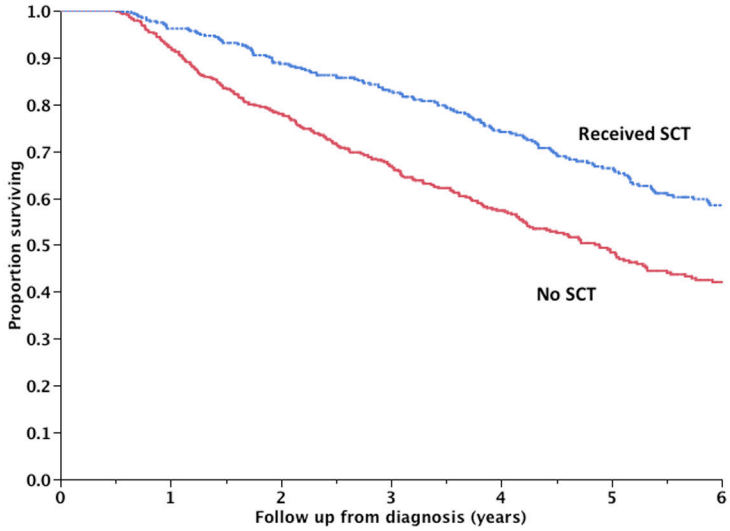

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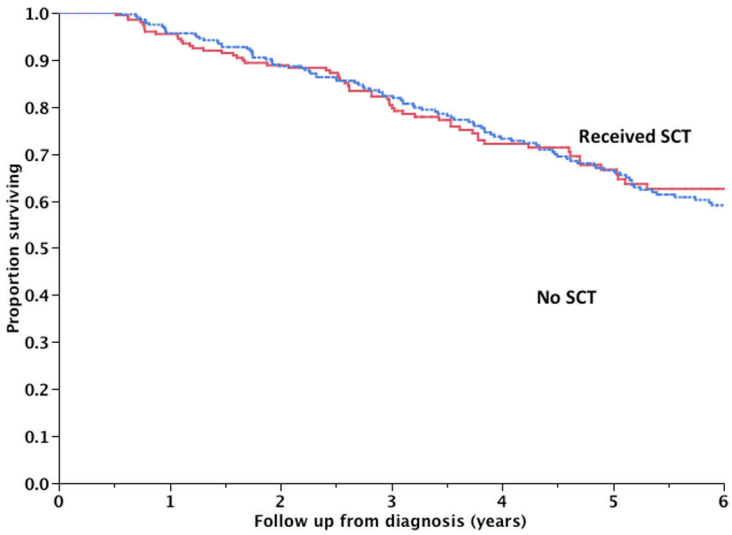
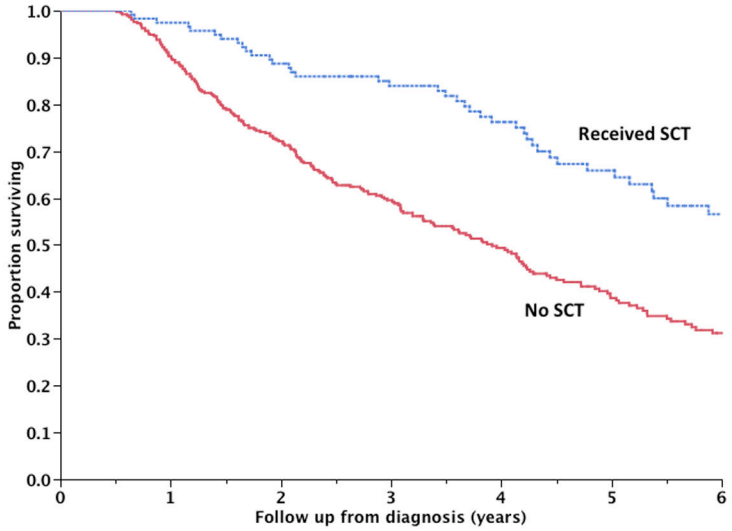


Figure 2D



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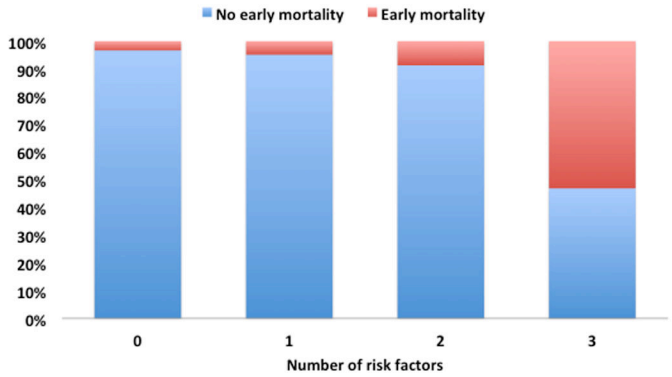

Figure 2.

Panel A shows the overall survival comparison between patients receiving one of the newer drugs (thalidomide, lenalidomide or bortezomib) as part of initial therapy and patients not receiving one of these regimens. ***Panel B*** shows the survival comparison between patients receiving an autologous stem cell transplantation versus those did not; with land marking at 6 months. Panels C and D demonstrates the survival comparison between patients receiving a stem cell transplant versus those who have not received a stem cell transplant among those 65 years or younger (***Panel C***) and those over 65 years (Panel D). Panel E shows the increasing risk of early mortality (1 year mortality) with increasing number of risk factors (identified age >70, serum albumin < 3.5 gm/dL, and serum beta 2 microglobulin > 6.5 mg/dL)

Figure 3A

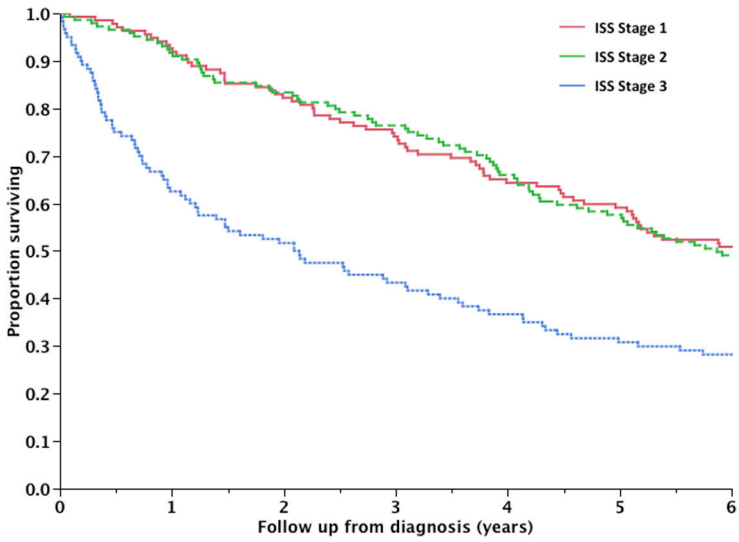

Figure 3B

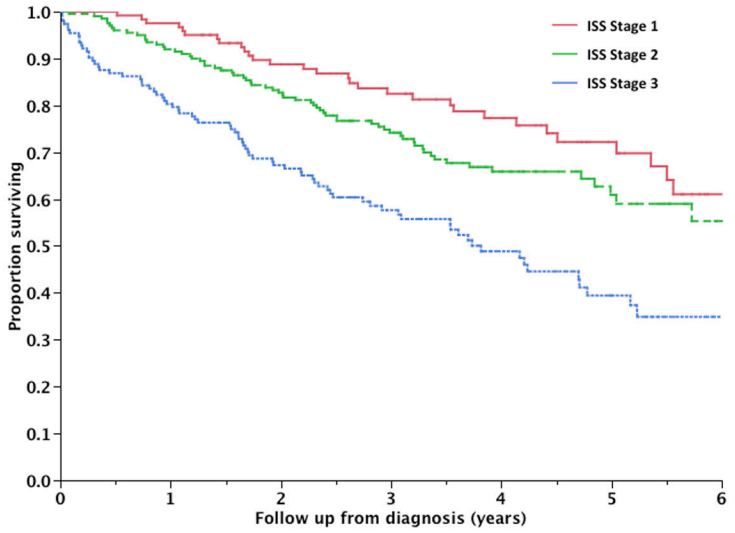

Figure 3C

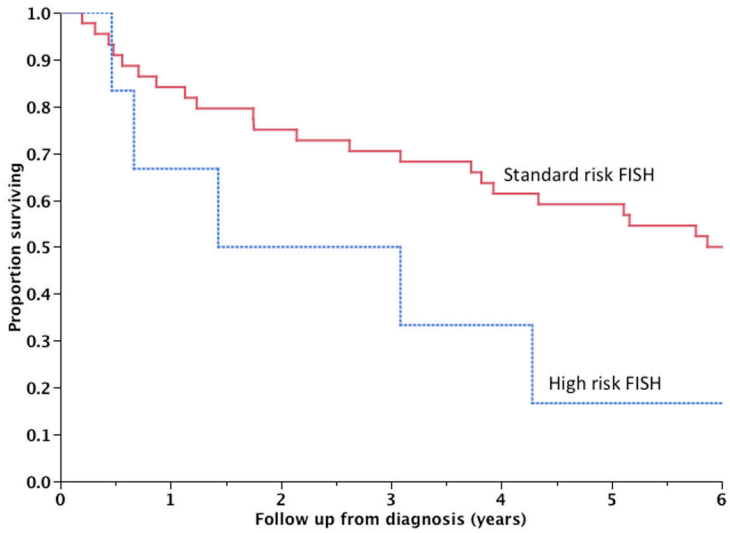

Figure 3D

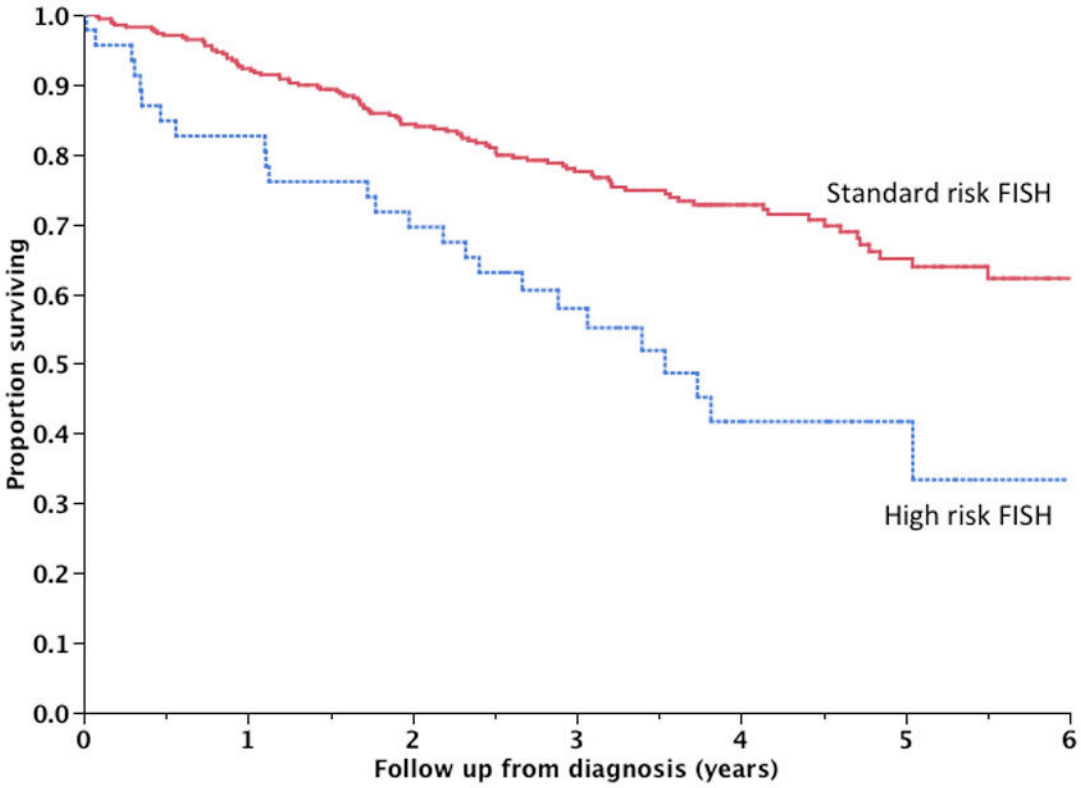

Figure 3.

Panel A and B shows the survival according to the International Staging System (ISS) among patients diagnosed during 2001–2005 (***Panel A***) and those diagnosed later (***Panel B***).

Panel C and D shows the survival according to the FISH based risk status among patients diagnosed during 2001–2005 (***Panel C***) and those diagnosed later (***Panel D***).

TABLE 1

Baseline characteristics

Characteristics	All patients (N=1038)	Group 1 (2001–2005; N=477)	Group 2 (2006–2010; N=561)
Age (years)*	66 (50, 79)	65 (50, 80)	66 (50, 78)
Age > 65	52%	50%	54%
Age > 75	19%	22%	17%
Gender: Male	59%	60%	58%
ISS Stage 1	30%	35%	26%
ISS Stage 2	39%	36%	42%
ISS Stage 3	31%	29%	32%
Serum creatinine (mg/dl)*	1.1 (0.8, 2.3)	1.2 (0.9, 2.5)	1.0 (0.7, 2)
Serum creatinine > 2.0 mg/dL	12%	14%	10%
Serum B2M (mg/dL)*	3.9 (2, 11.4)	3.8 (2, 11.7)	3.9 (2.2, 10.7)
Serum LDH (IU/dL)*	158 (110, 269)	155 (107, 265)	161 (112, 272)
Serum Calcium (mg/dL)*	9.5 (8.5, 10.5)	9.5 (8.4, 10.5)	9.6 (8.6, 10.6)
Hemoglobin (g/dL)*	10.8 (8.6, 13.6)	10.7 (8.6, 13.3)	10.9 (8.6, 13.8)
BMPC%	50 (18, 80)	50 (18, 80)	50 (15, 84)
IgG (g/dL)*	2.0 (0.3, 6.7)	2.0 (0.3, 6.2)	2.0 (0.3, 6.8)
IgA (mg/dL)*	51 (11, 3200)	51 (12, 3400)	52 (10, 2900)
Kappa: Lambda	66:34	65:35	67:33
Light chain MM	17%	17%	17%
High Risk MM#	12%	12%	12%

*Represent median (10^{th} percentile, 90^{th} percentile)

#defined as presence of (t(4;14), t(14;16), t(16;20), or del 17p in the absence of any trisomy

Table 2

Commonly used initial therapy regimens and frequency

Regimen	2001–2005	2006–2010
VAD	2%	(1 patient)
Dexamethasone	45%	6%
Melphalan-Prednisone	21%	3%
Thalidomide-Dexamethasone	16%	3%
Other thalidomide-based regimen	0%	3%
Lenalidomide-Dexamethasone	11%	52%
Other lenalidomide-based regimen	0%	10%
Bortezomib-Dexamethasone	1%	7%
Other bortezomib-based regimen	0%	5%
VTD	0%	2%
VRD	0%	4%

Abbreviations: VAD Vincristine, Adriamycin and Dexamethasone; VTD Bortezomib (Velcade), Thalidomide and Dexamethasone; VRD Bortezomib (Velcade), Lenalidomide (Revlimid) and Dexamethasone

Table 3

Impact of various prognostic factors on survival during the two time periods

Prognostic variable	2001–2005		2006–2010	
	Relative risk	***P***	***Relative risk***	***P***
Age (> 65 years)	2.2 (1.8, 2.8)	<0.001	1.8 (1.3, 2.4)	<0.001
Serum creatinine (> 2.0 mg/dL)	1.5 (1.1, 2.0)	0.008	2.2 (1.4, 3.1)	<0.001
ISS				
Stage 2 (vs. Stage 1)	0.97 (0.7, 1.3)	0.8	1.4 (0.9, 2.2)	0.08
Stage 3 (vs. Stage 1)	1.7 (1.3, 2.2)	<0.001	2.7 (1.8, 4.1)	<0.001
Serum Calcium (>11.5 mg/dL)	2.1 (1.2, 3.4)	0.008	3.0 (1.4, 5.7)	0.01
LDH (> 222 IU/dL)	2.0 (1.4, 2.7)	<0.001	2.7 (1.8, 3.8)	<0.001
High Risk FISH*	2.4 (0.8, 5.8)	NS	2.3 (1.5, 3.5)	<0.001
High Risk FISH#	2.8 (1.1, 6.3)	0.04	1.5 (0.99, 2.2)	0.05
PCLI > 1%	1.5 (1.2, 1.9)	<0.01	1.2 (0.9, 1.7)	NS
PCLI > 3%	1.5 (1.01, 2.2)	0.04	2.0 (1.3, 2.9)	0.002

*defined as presence of (t(4;14), t(14;16), t(16;20), or del 17p in the absence of any trisomy

#defined as presence of (t(4;14), t(14;16), t(16;20), or del 17p (traditional definition, no reference to trisomy)