In the Age of Novel Therapies, What Defines High-Risk Multiple Myeloma?

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Key Words

Chromosomal abnormalities, risk stratification, thalidomide, bortezomib, lenalidomide, allogeneic stem cell transplantation

Abstract

Multiple myeloma is characterized by clinical and biologic heterogenicity. Recently, genetic analysis has provided predictable prognosis across different types of treatment. These advances have allowed patients to be categorized into different risk groups and have been particularly useful in defining a high-risk group with short survival after standard- and high-dose chemotherapies. Preliminary studies have shown promising outcomes after the use of novel agents, such as bortezomib, thalidomide, and lenalidomide in high-risk patients, including those eligible for autologous stem cell transplantation and those who cannot or will not undergo transplantation. The application of risk-based therapy and the potential of the new agents to abrogate the influence of adverse prognostic features may improve outcomes in these patients. (*JNCCN* 2010;8[Suppl 1]:S28–S34)

Multiple myeloma (MM) is a clinically and pathophysiologically heterogeneous disease, as evidenced by variable response to treatment and variation in survival from a few months to more than 10 years. Nationwide U.S. data show that approximately 20% of patients survive longer than 10 years, irrespective of therapy.[1,2] Genetic variations among myeloma cells appear to underlie much of the heterogeneity in clinical outcomes.

Several groups have reported on the prognostic capability of genetic information in MM, which has led to re-evaluation of the definition of high-risk disease.[3,4]

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The use of nonchemotherapeutic antimyeloma agents is also driving efforts for improved prognostication. Recent data suggest that agents such as thalidomide, bortezomib, and lenalidomide may neutralize the effects of negative prognostic factors. An effective means of risk stratification is required so that patients with poor risk may be offered more aggressive treatment or be entered into clinical trials of novel agents as first-line therapy. This article discusses evolving systems for risk stratification and the potential of novel agents to improve outcomes in high-risk patients newly diagnosed with MM.

Evaluation of Genetic Changes

Plasma cells in MM harbor multiple and complex chromosomal abnormalities. Studies in the past 7 to 8 years have shown the prognostic value of genetic aberrations, and the assessment of chromosomal abnormalities is an additional parameter that can refine the identification of high-risk patients.

The different techniques currently used to detect genetic aberrations are conventional karyotyping, fluorescence in situ hybridization (FISH), and microarray technology.[5] Nearly all patients with MM have abnormal chromosomes according to FISH (deletions, aneuploidy, and translocations), but standard metaphase analysis identifies aberrant karyotypes in approximately 30% of patients.[6] Any abnormality detected conventionally identifies a subgroup with a higher proliferative rate and worse prognosis.

Several chromosomal changes have been associated with shorter survival. The most widely recognized poor prognosticators of survival are deletions of chromosome 13 or its long arm (del[13]), translocations of the heavy-chain gene on chromosome 14 (t[4;14] or t[14;16]), and deletion of *p53* on chromosome 17p13 (del[17p]). Deletion or structural anomalies of chromosome 13 are

detected in approximately 50% of patients with an abnormal karyotype and in 10% to 20% of patients overall. Patients with chromosome 13 anomalies in their metaphase cells have shorter survival and lower treatment response rates. The effect of del(13) on prognosis is greater when it is detected with karyotype analysis in metaphase cells than with interphase FISH.[5,7–9] Recent data suggest that the prognostic significance of del(13) may depend on its association with t(4;14), del(17p), or a high serum level of β_2-microglobulin (β_2M).[9]

Chromosome translocations involving the immunoglobulin heavy-chain gene locus are detectable in 60% to 75% of patients with MM according to FISH. Translocations that have prognostic significance include t(4;14), t(14;16), t(11;14), and t(6;14). Of these, t(4;14) (detected in 15%–20% of patients) and t(14;16) (present in 2%–10% of patients) are unfavorable prognostic factors for patients with MM treated with either conventional or high-dose therapy (HDT).[5,6,8,10] By contrast, t(11;14) (detected in 15%–20% of patients) characterizes a group of patients with neutral or somewhat favorable prognosis.[8,9]

Deletion of chromosome 17p13, present in 10% of patients, confers poorer survival. Patients with this deletion who undergo HDT followed by autologous stem cell transplantation (ASCT) have significantly shorter progression-free and overall survival than patients without this deletion.[6–8]

Aneuploidy occurs frequently in MM cells, and ploidy status has a significant impact on prognosis. Hypoploidy is associated with more aggressive disease and shorter survival. Hyperdiploid MM has a lower frequency of immunoglobulin heavy-chain translocations and is associated with good prognosis.[5,9]

Although chromosomal anomalies have a high impact on survival, they must be evaluated in the context of other parameters, especially the β_2M level. For example, subsets of patients with high-risk genetics, such as t(14;4) or del(17p), but with low β_2M level may have a similar or only marginally worse prognosis than other patients.[9]

A few teams have recently investigated the role of gene expression profiling (GEP) in the prognostication of myeloma, and several molecular classification systems have been proposed based on this technique.[11–13] Although GEP is useful for risk stratification, it is currently limited by a lack of a uniform platform and widespread availability, and thus is not easily translated into clinical practice.

Table 1 Recommended Classification of High-Risk Myeloma

High Risk (25%)	Good Risk (75%)*
Any of the following:	Absence of high-risk features and presence of any of the following:
t(4;14) according to FISH	Hyperdiploidy
t(14;16) or t(14;20) according to FISH	t(11;14) according to FISH
Del 17q13 according to FISH	t(6;16) according to FISH
Deletion 13 or aneuploidy according to metaphase analysis	
Plasma cell labeling index > 3%	

Abbreviations: FISH, fluorescence in situ hybridization.
*Patients should be considered to be truly low-risk if genetic markers are accompanied by a β_2-microglobulin level less than 5.5 mg/L, lactate dehydrogenase less than 250 U/L, and/or a plasma cell labeling index less than 1%. Similarly, the presence of β_2-microglobulin level less than 3.5 mg/L may favorably modify the course for patients with otherwise high-risk genetics.
Reprinted with permission from Macmillan Publishers Ltd. 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;21:529–534.

Risk Stratification

Genetic changes display such a high prognostic value that myeloma experts have recently recommended including cytogenetic and FISH evaluations in a risk stratification system (Table 1).[4,14] Routine molecular genetic testing is recommended for all patients with MM to identify the 25% with high-risk disease in whom conventional therapies perform poorly. The recommended basic test panel includes FISH detection of t(4;14), t(14;16), and del(17q); cytogenetic detection of del(13); and determination of serum β_2M, lactate dehydrogenase, or plasma cell labeling index as surrogate markers of tumor cell proliferation.

This risk-stratification model in Table 1 forms the basis of the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART), an evidence-based algorithm of treatment decision-making that was developed at the Mayo Clinic for patients with newly diagnosed MM.[15] In general, these high-risk features define a population of 25% to 30% of patients who have median survival of 2 to 3 years, even with stem cell transplantation, compared with

Table 2 Selected Studies of New Agents in Newly Diagnosed High-Risk Patients Eligible for High-Dose Therapy/Autologous Stem Cell Transplantation

First Author	No. of Patients	Patient Population	Treatment	Results
Bortezomib				
Dispenzieri et al.[19]	44	Patients with high-risk newly diagnosed myeloma (del[13q], PCLI > 1%, t[4;14] or β_2M > 5.5 mg/L)	Bortezomib for induction and maintenance	Response rate (> PR): • All = 48% • PCLI > 1%: 47% • β_2M > 5.5 mg/L: 45% • del(13q): 33% • t(4;14): 50% After median follow-up of 41.6 months: • 1-y PFS/OS: 50%/88% • 2-y PFS/OS: 28%/76%
Knop et al.[20]	200	Newly diagnosed myeloma β_2M: 3.75 ± 3.38 mg/L del(13): 55 (28%) del(17p): 20 (10%) t(4;14): 16 (8%)	Bort-dex-cyclophosphamide	Response rate on day 63 ORR: 84% Normal cytogenetics: 86% Abnormal cytogenetics: 82% del(13): 82% del(17p): 70% t(4;14): 94%
Lenalidomide				
Kapoor et al.[21]	100	High-risk: at least 1 of the following: hypodiploidy, del(13), del(17p), t(4;14), t(4;16), or PCLI ≥ 3% Standard-risk: absence of all high-risk features	Len-dex (low- or high-dose)	Response rates: • CR + VGPR: high-risk, 38%; standard-risk, 45% • ≥ PR: high-risk, 81%; standard-risk, 89% Median PFS: high-risk, 18.5 months; standard-risk, 36.5 months Median OS: not reached for either group
Zonder et al.[22]	198	AK Len-dex: 13/54 Dex: 12/43 FISH-defined HRCA (del[13] or del[17p]) Len-dex group: 8/37 Dex group: 11/45	Len-dex vs. placebo-dex	Estimated 1-y PFS (with AK vs. without): • Len-dex: 54% vs. 86% (P = NS) • Dex: 27% vs. 67% (P = .008) Estimated 1-y PFS (with HRCA vs. without): • Len-dex: 100% vs. 71% (P = NS) • Dex: 55% vs. 57% (P = NS) Estimated 1-y OS (with HRCA vs. without): • Len-dex: 80% vs. 100% (P = NS) • Dex: 88% vs. 100% (P = NS)
Kapoor et al.[23]	125	High baseline PCLI (≥ 1%) vs. low baseline PCLI (< 1%)	Len-dex vs. TD	Median PFS (high PCLI vs. low PCLI) • Len-dex: 2.3 vs. 3.1 y (NS) • TD: 1.3 vs. 2.3 y (P = .01) Median OS • Len-dex: not reached for either group • TD: 2.3 vs. 6.9 y (P = .02)
Thalidomide				
Zangari et al.[24] Waheed et al.[25]	668	Patients with or without cytogenetic abnormalities by metaphase analysis	TT2 protocol (induction, tandem transplantation, consolidation, maintenance) with thal vs. TT2 protocol without thal	5-y follow-up (TT2 + thal vs. TT2 without thal) Median EFS: • With CA: 3.7 vs. 2.5 y (P = .03) • Without CA: 6.3 vs. 5.4 y (P = .04) Median OS: • With CA: NR vs. 4.1 y (P = .04) • Without CA: NR vs. NR 81-month follow-up (TT2 + thalidomide vs. TT2 without thalidomide) 6-y EFS • With CA: 38% vs. 20% (P = .008) • Without CA: 56% vs. 45% (P = .02) 6-y OS • With CA: 53% vs. 35% (P < .001) • Without CA: 70% vs. 68% (P = NS)
Combinations				
Cavo et al.[26]	474 (464 evaluable)	ISS II + III: 54%–56% del(13): 46%–47% t(4;14): 19%–20% del(17p): 7%–8%	VTD vs. TD	≥ nCR rate after induction: • ISS III: VTD, 24%; TD, 6% (P = .03) • del(13q): VTD, 39%; TD, 12% (P < .001) • t(4;14): VTD, 40%; TD, 9% (P < .001) • del(17p): VTD, 27%; TD, 0% (P < .001)

Table 2 Selected Studies of New Agents in Newly Diagnosed High-Risk Patients Eligible for High-Dose Therapy/Autologous Stem Cell Transplantation (cont.)

First Author	No. of Patients	Patient Population	Treatment	Results
Combinations (cont'd.)				
Pineda-Roman et al.[27]	303	ISS II: 32% ISS III: 21% CA: 33% GEP-defined high risk: 15% GEP subgroup MS: 11%	TT3 protocol (induction and consolidation with VTD-PACE; maintenance with VTD) vs. TT2 protocol (historical controls)	2-y outcomes (TT3 vs. TT2 + thalidomide) CR duration • Low-risk: 95% vs. 84% (P = .01) • High-risk: 61% vs. 54% (P = NS) • *MMSET* risk subgroup: 89% vs. 46% (P = .004) EFS • Low-risk: 89% vs. 85% (P = .04) • High-risk: 60% vs. 35% (P = NS) • *MMSET* risk subgroup: 84% vs. 57% (P = NS) OS • Low-risk: 90% vs. 89% (P = NS) • High-risk: 70% vs. 46% (P = NS) • *MMSET* risk subgroup: 97% vs. 67% (P = .01)
Richardson et al.[28]	63	Patients with newly diagnosed MM ISS II/III: n = 31 del(13): n = 7 t(4:14): n = 10	Len + bort + dex for up to eight 21-day cycles	Response ORR/≥ VGPR after median of 10 cycles All patients: 98%/71% del(13)$^{+}$: 86%/57% del(13)$^{-}$: 100%/75% t(4;14)$^{+}$: 100%/70% t(4;14)$^{-}$: 98%/73% ISS I: 97%/51%, ISS II : 100%/57%, ISS III: 100%/80%
Landau et al.[29]	34	Patients with high-risk MM	Bort + liposomal dox + dex followed by thal + dex	Any response: del(13)$^{+}$: 91% del(13)$^{-}$: 70% t(4;14)$^{+}$: 100% t(4;14)$^{-}$: 75% del(p53)$^{+}$: 100% del(p53)$^{-}$: 76%

Abbreviations: AK, abnormal karyotype; β_2M, β_2-microglobulin; bort, bortezomib; CA, chromosomal abnormality; CR, complete response; dex, dexamethasone; dox, doxorubicin; EFS, event-free survival; FGFR3, fibroblast growth factor receptor 3; FISH, fluorescence in situ hybridization; GEP, gene expression profiling; HRCA, high-risk cytogenetic abnormality; ISS, International Staging System; len, lenalidomide; MM, multiple myeloma; MMSET, multiple myeloma SET domain; nCR, near complete response; NR, not reported; NS, not significant; ORR, overall response rate; OS, overall survival; PACE, cisplatin, doxorubicin, cyclophosphamide, etoposide; PCLI, plasma cell labeling index; PFS, progression-free survival; PR, partial response; thal, thalidomide; TD, thalidomide-dexamethasone; VGPR, very good partial response; VTD, bortezomib-thalidomide-dexamethasone.

more than 6 to 7 years for patients with standard-risk MM.[16] Furthermore, identifying the other 75% of patients as standard risk allows them to receive appropriate treatment with minimal toxicity.

Emerging data suggest that novel therapies and combinations may ameliorate the adverse influence of these poor-risk features, underscoring the importance of including genetics into risk-stratification schemes. Current NCCN guidelines include cytogenetic and FISH evaluation as part of the initial diagnostic workup but note that further data are needed before cytogenetic information can be incorporated into patient management.[17]

Outcomes With Novel Agents

A major application of genetic stratification is in the selection of candidates for HDT-ASCT. Several large studies have shown that patients defined as being at high risk genetically do not develop durable responses to HDT as currently practiced, and many experience early relapse after ASCT.[7–9,18] High-risk patients are therefore considered appropriate candidates for alternative approaches, including early incorporation of novel agents. Clinical trial data suggest that in patients with MM who are eligible for transplantation, newer agents may be able to overcome the adverse influence of cytogenetic abnormalities (Table 2).[19–29]

Two major combinations have emerged as treatment options for elderly patients and others who will not undergo transplantation: melphalan-prednisone (MP) plus an immunomodulatory agent, and MP plus bortezomib. Both of these approaches have resulted in outcomes superior to those with MP alone and are recommended induction therapies (NCCN category 1 recommendation) in patients ineligible for transplantation.[17] These new combinations have also shown efficacy in high-risk patients ineligible for transplantation (Table 3).[30–33]

Role of ASCT

The introduction of reduced-intensity conditioning

Table 3 Selected Studies of New Agents in Patients With Newly Diagnosed High-Risk Disease Ineligible for High-Dose Therapy/Autologous Stem Cell Transplantation

First Author	No. of Patients	Patient Population	Treatment	Results	
Mateos et al.[30,31]	60	Elderly patients del(13): n = 13 IgH translocation: n = 8	Bort-melphalan-prednisone	Response rate: Rb del: 100% IgH tr: 88% TTP (months): β_2M < 3.5 mg/L: 23 ISS stage I/II: 27 Rb del: 25 (IgH tr$^-$)/no RB del: 29	 No Rb del: 66% No IgH tr: 82% β_2M ≥ 3.5 mg/L: 29 ISS stage III: 24 No Rb del: NR (IgH tr)$^+$/Rb del: 23
San Miguel et al.[32]	682	Elderly patients ISS I: 19% ISS II: 47% ISS III: 34%–35% KPS ≤ 70%: 33%–35% Bort group: High-risk cytogenetics [t(4;14)/t(14;16)/del(17p)]: n = 26 Standard-risk: n = 142	Bort-melphalan-prednisone vs. melphalan-prednisone	Bort group: High-risk vs. standard-risk patients: CR: 28% in both TTP: *P* = .55 OS: *P* = .99	
Palumbo et al.[33]	54	Elderly patients Median age: 71 y ISS I: 34% ISS II: 32% ISS III: 32% β_2M ≥ 3.5 mg/mL: 57% del(13): 38% Data missing: 21%	Lenalidomide-melphalan-prednisone	1-y EFS: β_2M < 3.5: 100% del(13): 85% t(4;14): 83%	 β_2M ≥ 3.5: 86% (*P* = .02) No del(13): 95% (*P* = NS) No t(4:14): 87.5% (*P* = NS)

Abbreviations: β_2M, β_2-microglobulin; bort, bortezomib; CR, complete response; EFS, event-free survival; NS, not significant; ISS, International Staging System; KPS, Karnofsky performance status; OS, overall survival; TTP, time to progression.

regimens with reduction in immediate transplantation-related mortality and stable engraftment has rekindled interest in allogeneic transplantation. In patients with poor-risk disease, nonmyeloablative conditioning regimens (mini-allogeneic transplantation) with or without donor lymphocyte infusions have resulted in excellent responses and stable engraftment, with lower transplantation-related mortality, although acute and chronic graft-versus-host disease remains a troubling complication.[34,35] In a prospective trial, the Intergroupe Francophone du Myélome studied ASCT followed by nonmyeloablative allotransplantation in patients with newly diagnosed MM who had both elevated β_2M and del(13),[36] then compared the results with data on patients with the same high-risk features but had no donor and had undergone tandem ASCT.[37] The median duration of overall (35 vs. 41 months) and progression-free survival (25 vs. 30 months) did not differ significantly between the regimens.[36]

Encouraging long-term follow-up results were recently reported for 102 patients who underwent ASCT followed by nonmyeloablative allogeneic hematopoietic stem cell transplantation from a human leukocyte antigen-identical sibling.[38] After a median follow-up of 6.3 years, the median overall survival was not reached, and estimated 5-year overall and progression-free survival were 64% and 36%, respectively. Although cytogenetic studies were not performed at specific times or using uniform methods, the authors reported that cytogenetics had no effect on the risk for relapse, suggesting that allogeneic transplantation may overcome adverse genetic prognostic features. A recent analysis of the prognostic impact of the most frequent genetic abnormalities in patients who underwent allogeneic transplantation showed that del(17p) was the only significant prognostic factor, with a negative impact on complete response and length of event-free survival.[39] In multivariate analyses, only del(13) and del(17p) significantly influenced the rate of relapse, whereas for event-free survival, only age and del(17p) remained negative prognostic factors. Major findings were that t(4;14) was not associated with a worse complete response rate or shorter event-free or overall survival, suggesting that the negative effect of t(14;4) might be overcome with allogeneic transplantation. These results may have implications for risk-adapted strategies.

Conclusions

Defining a high-risk cohort of patients with MM with short survival regardless of treatment will be helpful in guiding management decisions. With the demonstrated adverse influence of chromosomal changes, various groups have endorsed a new risk stratification model that incorporates recently defined independent prognostic markers of underlying myeloma cell biology. Efforts have focused on defining a high-risk group that might merit a different management approach, such as early treatment with novel agents. The proposed risk stratification system remains a global stratification and is not therapy-based, although ongoing trials may uncover risk factors specific for individual therapies. The general agreement is that no definitive treatment can currently be mandated based on the presence of risk factors.[14] The use of genetic information for stratifying risk and making treatment decisions continues to be explored in clinical trials and will likely play a greater role in patient care in the near future.

New therapies with novel mechanisms of action may benefit patients for whom other therapies fail. Preliminary reports from several groups show high response rates with use of bortezomib, lenalidomide, and thalidomide in both the transplantation and nontransplantation settings in high-risk patients, suggesting that these new agents may ameliorate the effects of adverse prognostic factors. Long-term follow-up and confirmation in prospective, comparative trials will be required to determine whether clinical benefit can be sustained.

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References

1. Rajkumar SV, Buadi F. Multiple myeloma: new staging systems for diagnosis, prognosis and response evaluation. Best Pract Res Clin Haematol 2007;20:665–680.
2. Horner MJ, Ries LAG, Krapcho M, et al. SEER Cancer Statistics Review, 1975–2006. Available at: http://seer.cancer.gov/csr/1975_2006. Accessed May 8, 2009.
3. Stewart AK, Fonseca R. Prognostic and therapeutic significance of myeloma genetics and gene expression profiling. J Clin Oncol 2005;23:6339–6344.
4. 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;21:529–534.
5. Fonseca R, Barlogie B, Bataille R, et al. Genetics and cytogenetics of multiple myeloma: a workshop report. Cancer Res 2004;64:1546–1558.
6. Dewald, GW, Therneau T, Larson D, et al. Relationship of patient survival and chromosome anomalies detected in metaphase and/or interphase cells at diagnosis of myeloma. Blood 2005;106:3553–3558.
7. Chang, H, Qi XY, Samiee S, et al. Genetic risk identifies multiple myeloma patients who do not benefit from autologous stem cell transplantation. Bone Marrow Transplant 2005;36:793–796.
8. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. Blood 2005;106:2837–2840.
9. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. Blood 2007;109:3489–3495.
10. Chang, H, Sloan S, Li D, et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. Br J Haematol 2004;125:64–68.
11. Shaughnessy JD Jr, Zhan F, Burington BE, et al. A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. Blood 2007;109:2276–2284.
12. Zhan F, Barlogie B, Mulligan G, et al. High-risk myeloma: a gene expression based risk-stratification model for newly diagnosed multiple myeloma treated with high-dose therapy is predictive of outcome in relapsed disease treated with single-agent bortezomib or high-dose dexamethasone. Blood 2008;111:968–969.
13. Decaux, O, Lode L, Magrangeas F, et al. Prediction of survival in multiple myeloma based on gene expression profiles reveals cell cycle and chromosomal instability signatures in high-risk patients and hyperdiploid signatures in low-risk patients: a study of the Intergroupe Francophone du Myélome. J Clin Oncol 2008;26:4798–4805.
14. International Myeloma Workshop. Guidelines for risk stratification in multiple myeloma. Report of the 2008 International Myeloma Workshop Consensus Panel 2. Available at http://www.mw-delhi09.com/spargoDocs/Consensuspaneltwo.pdf. Accessed June 10, 2009.
15. 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;82:323–341.
16. Rajkumar SV, Kyle RA. Multiple myeloma: diagnosis and treatment. Mayo Clin Proc 2005;80:1371–1382.
17. Anderson KC, Alsina M, Bensinger W, et al. NCCN clinical practice guidelines in oncology: multiple myeloma, v2.2010. Available at www.nccn.org. Accessed July 31, 2009.
18. Fonseca R. Strategies for risk-adapted therapy in myeloma. Hematology Am Soc Hematol Educ Program 2007;304–310.
19. Dispenzieri, A, Jacobus S, Vesole DH, et al. Primary therapy with bortezomib—the role of induction, maintenance, and re-induction in patients with high risk myeloma: update of results from E2A02 [abstract]. Presented at the 2008 American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California. Abstract 1738.

20. Knop S, Liebisch P, Wandt H, et al. Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: results of an interim analysis of the German DSMM Xia trial [abstract]. Presented at the 2009 American Society of Clinical Oncology Annual Meeting; May 29–June 2, 2009; Orlando, Florida. Abstract 8516.

21. Kapoor P, Kumar S, Fonseca R, et al. Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone. Blood 2009;114:518–521.

22. Zonder J, Crowley J, Bolejack V, et al. A randomized Southwest Oncology Group study comparing dexamethasone to lenalidomide + dexamethasone (LD) as treatment of newly diagnosed multiple myeloma: impact of cytogenetic abnormalities on efficacy of LD, and updated overall study results [abstract]. Presented at the 2008 American Society of Clinical Oncology Annual Meeting; May 30–June 3, 2008; Chicago, Illinois. Abstract 8521.

23. Kapoor P, Kumar S, Greipp PR, et al. Prognostic impact of the plasma cell labeling index (LI) in newly diagnosed myeloma patients treated with thalidomide-dexamethasone (thal/dex) or lenalidomide-dexamethasone (len/dex) [abstract]. Presented at the 2008 American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California. Abstract 1729.

24. Zangari M, van Rhee F, Anaissie E, et al. Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1. Br J Haematol 2008;141:433–444.

25. Waheed S, Shaughnessy J, Szymonifka, J, et al. Benefit of thalidomide in Total Therapy 2 (TT2) of multiple myeloma exhibiting both cytogenetic abnormalities and low risk by gene expression profiling [abstract]. Presented at the 2009 American Society of Clinical Oncology Annual Meeting; May 29–June 2, 2009; Orlando, Florida. Abstract 8590.

26. Cavo, M, Testoni N, Terragna C, et al. Superior rate of complete response with up-front Velcade-thalidomide-dexamethasone versus thalidomide-dexamethasone in newly diagnosed multiple myeloma is not affected by adverse prognostic factors, including high-risk cytogenetic abnormalities [abstract]. Presented at the 2008 American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California. Abstract 1662.

27. Pineda-Roman M, Zangari M, Haessler J, et al. Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. Br J Haematol 2008;140:625–634.

28. Richardson P, Lonial S, Jakubowiak A, et al. Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: encouraging efficacy in high risk groups with updated results of a phase I/II study [abstract]. Presented at the 2008 American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California. Abstract 92.

29. Landau H, Hassoun H, Cohen A, et al. Sequential administration of bortezomib, liposomal doxorubicin and dexamethasone followed by thalidomide and dexamethasone results in rapid control of untreated high-risk multiple myeloma and improves depth of response [abstract]. Presented at the 2008 American Society of Hematology Annual Meeting; December 6–9, 2008; San Francisco, California. Abstract 3712.

30. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood 2006;108:2165–2172.

31. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression. Haematologica 2008;93:560–565.

32. San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med 2008;359:906–917.

33. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA—Italian Multiple Myeloma Network. J Clin Oncol 2007;25:4459–4465.

34. Badros A, Barlogie B, Morris C, et al. High response rate in refractory and poor-risk multiple myeloma after allotransplantation using a nonmyeloablative conditioning regimen and donor lymphocyte infusions. Blood 2001;97:2574–2579.

35. Badros A, Barlogie B, Siegel, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. J Clin Oncol 2002;20:1295–1303.

36. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474–3480.

37. Moreau P, Hullin C, Garban F, et al. Tandem autologous stem cell transplantation in high-risk de novo multiple myeloma: final results of the prospective and randomized IFM 99-04 protocol. Blood 2006;107:397–403.

38. Rotta M, Storer BE, Sahebi F, et al. Long-term outcome of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. Blood 2009;113:3383–3391.

39. Schilling G, Hansen T, Shimoni A. et al. Impact of genetic abnormalities on survival after allogeneic hematopoietic stem cell transplantation in multiple myeloma. Leukemia 2008;22:1250–1255.